

**IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF VIRGINIA  
Norfolk Division**

**AVENTIS PHARMA DEUTSCHLAND GMBH and  
KING PHARMACEUTICALS, INC.,  
Plaintiffs**

**v.**

**Civil Action No. 2:05cv421**

**LUPIN LTD. and  
LUPIN PHARMACEUTICALS, INC.  
Defendants.**

**MEMORANDUM OPINION AND ORDER**

This case involves an action for patent infringement and counterclaims of invalidity with respect to Altace, the marketing name of a pharmaceutical compound known as Ramipril “substantially free of other isomers.” Altace is protected by U.S. Patent No. 5,061,722 (the ‘722 patent), which was issued on October 29, 1991 and will expire on October 19, 2008. Interestingly enough, the ‘722 patent is a subsequent patent to a patent known as the ‘258 patent, which was approved by the Food and Drug Administration (“FDA”) for the original marketing and production of Altace.

On June 5, 2006, this Court issued summary judgment finding infringement based on the doctrine of equivalents. Accordingly, only the defendants’ defenses to infringement remain. After a bench trial and for the reasons stated herein, the Court **FINDS** that the ‘722 patent is valid and that Lupin’s defenses to infringement fail. The Court reaches this decision reluctantly. If the standard applied to Lupin’s defenses that the ‘722 patent was invalid had been by a preponderance of the evidence instead of clear and convincing evidence, the Court might have determined this case in

Lupin's favor. Unfortunately for Lupin, however, the standard is clear and convincing evidence, and it was unable to meet this heavy burden.

The Court is also of the view that it lacked the tools necessary to address what it perceives as the most problematic issue in this case, namely that Aventis/King has been able to effectively extend its patent protection for Altace by means of either clever maneuverings or fortuitous happenstance before the Patent and Trademark Office ("PTO") and the FDA. The Court details this in the Findings of Fact infra, but the short version is as follows.

Aventis, by means of a patent (the "258 patent") that it licensed from the Schering Corporation, obtained FDA approval to market Ramipril using the trade name Altace. It also obtained an extension of the '258 patent from the PTO. The '258 patent has expired, and Lupin believes it should be able to gain FDA approval to market a generic version of Altace for this reason. The '722 patent, however, now stands in Lupin's way. Aventis obtained the '722 patent after the '258 patent issued and strenuously maintains that it – not the '258 patent – discloses Ramipril substantially free of other isomers (or Altace). According to Aventis, this is the "active ingredient" in Altace. In other words, when it suited Aventis' needs, it relied on the '258 patent to gain FDA approval for Altace and requested an extension of the '258 patent before the PTO. Now that the '258 patent has expired, however, it relies on the '722 patent to prevent generic competition. While this concerns the Court, this is not to say that Aventis necessarily acted inequitably; rather, the timeline of patent approvals now works in Aventis' favor. Ultimately, the means of attacking the validity of a patent – anticipation, obviousness, inequitable conduct, enablement, etc. – do not adequately address such a circumstance because the conduct in question is not before the Patent Office but is before the FDA. Considering that the validity of a patent may only be challenged under the clear and convincing standard, the Court thus reluctantly finds for Aventis/King.

## **I. Overview**

### **A. The Parties**

Aventis Pharma Deutschland GMBH (“Aventis”) is the current holder of the ‘722 patent<sup>1</sup>; King Pharmaceuticals (“King”) is the exclusive licensee of the ‘722 patent, marketing Ramipril under the trade name Altace. Aventis and King are the plaintiffs in this case (collectively referred to as “Aventis/King”). Lupin Ltd., a generic drug company, and Lupin Pharmaceuticals, Inc. are the defendants (collectively referred to as “Lupin”).

### **B. Procedural History**

This action arose on July 19, 2005 when Aventis/King brought a two-count suit against Lupin for patent infringement and inducement of infringement with respect to the ‘722 patent. Prior to this time, on March 18, 2005, Lupin submitted an “Abbreviated New Drug Application” (“ANDA”) with “Paragraph IV certification” to the FDA seeking approval to market generic versions of Ramipril capsules.<sup>2</sup> Pursuant to 35 U.S.C. § 271(e)(2)(A), this filing allowed Aventis/King to bring “a legal action for patent infringement before the generic drug maker has begun marketing [the drug].” SmithKline Beecham Corp. v. Geneva Pharm., Inc., 287 F. Supp.2d 576, 582 (E.D. Penn. 2002). If the original patent owner brings suit, as Aventis did here, “then [FDA] approval may not be made effective until the court rules that the patent is not infringed or until the expiration of (in general) 30 months, which ever first occurs.” Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 677-78 (1990).

The ‘722 patent at issue has five claims. The parties agreed that only claim 1 required construction. Claim 1 reads in its entirety as follows, with the portions of the claim requiring

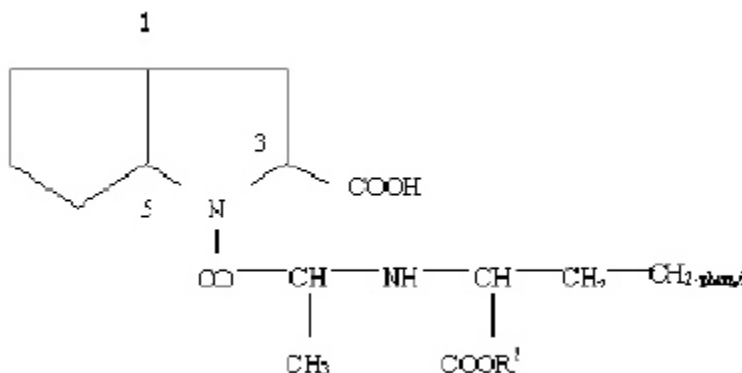
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<sup>1</sup>As explained infra, Aventis also was the exclusive licensee of the ‘258 patent.

<sup>2</sup>This Court explained the ANDA process in more detail in Aventis Pharma Deutschland GMBH v. Lupin Ltd., 403 F. Supp.2d 484, 486 (E.D. Va. 2005).

construction bolded:

A **compound** of the formula



or a physiologically acceptable salt thereof, wherein R2 is hydrogen, methyl, ethyl, or benzyl, and wherein hydrogen atoms on the ring carbon atoms in the 1- and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3-position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration, **said compound or salt being substantially free of other isomers.**

‘722 patent.

On May 5, 2006, this Court held a Markman Hearing. On May 11, 2006, this Court entered a claim construction order construing the terms “a compound” and “said compound or salt being substantially free of other isomers” found in claim 1 of the ‘722 patent. See Claim Construction Order Dated May 11, 2006 (Doc. 93). It found that “a compound” is “a fairly broad term meaning a chemically distinct substance formed by union of two or more ingredients (as elements) in definite proportion by weight and definite structural arrangement.” Id. at 1. It also found that “said compound or salt being substantially free of other isomers” means that “[R]amipril, the ‘said compound,’ is largely but not necessarily free of other isomers. In other words, ‘substantially free

of other isomers' qualifies the compound by indicating that it may not be 100% pure or 100% free of other isomers." Id. at 2.

On June 5, 2006, based on the doctrine of equivalents, this Court granted Aventis/King's motion for summary judgment on infringement subject to the condition that the '722 patent is found valid. Given this decision, Aventis/King's primary task in this case became to rebut Lupin's various defenses to infringement. Lupin first attacked the validity of the '722 patent, arguing anticipation under 35 U.S.C. § 102(a), (b), (e) and/or (g); obviousness under 35 U.S.C. § 103; enablement under 35 U.S.C. § 112, ¶ 1; and lack of written description under 35 U.S.C. § 112 ¶ 1. In addition, Lupin maintained that the '722 patent was unenforceable due to Aventis' alleged inequitable conduct before the PTO. Finally, Lupin asserted the defenses of equitable estoppel and prosecution laches.

On June 6, 2006, this Court held a bench trial. On June 14, 2006, at the conclusion of Lupin's case, the Court granted Aventis/King's motion for judgment as a matter of law with respect to Lupin's inequitable conduct defense. The Court overruled the motion with respect to obviousness and reserved ruling with respect to anticipation, enablement, and prosecution laches. On June 20, 2006, the Court granted Aventis/King's motion for judgment as a matter of law with respect to prosecution laches.

On June 26, 2006, the parties submitted post-trial briefs. The parties submitted their replies on July 3, 2006. The Court heard closing arguments on July 13, 2006. Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court now states its findings of fact and conclusions of law. The Court will emphasize its findings that it concludes are particularly relevant to this case.

## **II. Findings of Fact**

**A. Background: Chemistry Concepts Relevant to this Case**

**1. A Person of Ordinary Skill in the Art**

In this case, the level of ordinary skill in the art is high. The Court **FINDS** that a person of ordinary skill in the art would be someone with a Ph.D. in chemistry or organic chemistry with knowledge of stereochemistry or have a similar amount of training in association with preparing chemical compounds in the pharmaceutical industry and stereochemistry. Such a person would be familiar with methods for preparing, isolating, and characterizing pharmaceutical compounds and have knowledge of stereochemistry.

**2. Stereochemistry**

Stereochemistry is a subfield of chemistry that is concerned with how molecules are oriented in three-dimensional space. Isomers or “stereoisomers” are important concepts in stereochemistry. A stereoisomer is a term that refers to chemical compounds that have the same constituent atoms but are arranged in a unique pattern. Stereoisomers, in other words, are molecules that have the same building blocks but differ in their spatial arrangement.<sup>3</sup>

Enantiomers are a pair of stereoisomers that are non-superimposable mirror images of each other. They are like left and right hands: facing each other, they each look like a reflection of the other, but placing one on top of the other reveals that their spatial orientations are different. Mosberg at 21: 14-18; Ganem at 175: 6-7. A racemate, or racemic mixture, has an equal mixture of two enantiomers. Mosberg at 23: 15-16. Diastereomers are stereoisomers that are not enantiomers. They are more different from each other than enantiomers are different from each other. In fact,

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<sup>3</sup>Stereoisomers are not constitutional isomers, which are isomers having the same molecular formula but their atoms are connected up in a different pattern. Ganem at 59: 24-25.

unlike enantiomers, diastereomers usually have different melting and boiling points. Ganem at 174: 13-25.

In stereochemistry, a stereocenter generally refers to a carbon atom that has four different types of atoms or groups of atoms attached to it. This type of stereocenter is known as a chiral carbon. Ganem at 173: 13-18. Chiral carbons can exist in two possible three-dimensional configurations, known as the “R-configuration” and the “S-configuration” pursuant to a set of rules known as the Cahn-Ingold-Prelog system. Ganem at 171-72: 25, 2-4. The Cahn-Ingold-Prelog system, which a person of ordinary skill in the art would know, allows a chemist to understand a compound’s three-dimensional shape simply by looking at how the structure is drawn on a piece of paper. The terms “S” and “R” are ways in which chemists describe a right-hand or left-hand version of a compound.

### 3. Compound Definitions and Structures

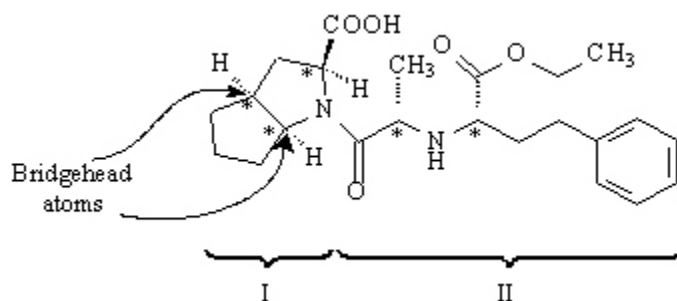
Because the parties compare the structures of Captopril, Enalapril, and Ramipril, three ACE-inhibiting compounds that reduce high blood pressure, see infra, a review of how the parties refer to and define portions of the compounds is necessary. A bicyclic compound is a compound that contains two rings that share atoms with each other. The shared atoms constitute a “bridge.” “Bridgehead carbons,” more specifically, are the carbon atoms at which the two rings meet in a bicyclic compound. Ramipril has a bicyclic ring that consists of two five-membered rings fused together.<sup>4</sup> The parties refer to this ring as a “5,5 bicyclic.”<sup>5</sup> The parties refer to where the rings meet

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<sup>4</sup>At times, the parties also refer to ring as the “proline ring.” An amino acid that has a five-membered ring is called a proline.

<sup>5</sup>A “6,5 bicyclic is where one ring has six sides (atoms) and the other, connecting ring has five sides (atoms).” Ganem at 399: 14-16.

as the “bridgehead.” The parties refer to the chain of compounds to which the “5,5 ” bicyclic is attached as the “side chain.” The following depiction illustrates these concepts:



As the illustration demonstrates, the Ramipril molecule may be characterized as having two parts: 1) the bicyclic ring which contains the bridgehead atoms, and 2) the side chain, which is attached to the bicyclic ring.

When groups or atoms lie on the same side of a plane in a molecule, they are referred to as “*cis*.” When groups or atoms lie on opposite sides of plane in a molecule, they are referred to as “*trans*.” The terms “*endo*” (or “*syn*”) and “*exo*” in a bicyclic ring system describe the relative orientation of groups attached to non-bridgehead carbons. A substituent – an atom or group of atoms – attached to a ring is *endo* (*syn*) if it is oriented toward the other ring, making a bowl or “V” shape. It is *exo* if the substituent is oriented away from it, giving it a flatter shape. Mosberg at 47: 3-4. In Ramipril, the bicyclic ring is known as “*cis, endo*” because all three chiral centers on the are in the S-configuration and because the ring is oriented in a certain way.

#### 4. Relevant Separation Techniques

Throughout this case, the parties refer to several separation techniques used by chemists. Fractional crystallization is a method of separating substances based on differences in their

solubility. If two or more substances are dissolved in a solvent, they will crystallize out of solution at different rates. Ganem at 61: 1-22. Chromatography generally is a method of passing a mixture through a solid substance. Thin layer chromatography (TLC) involves passing a solution through a thin layer of absorbent material. Column chromatography involves passing a substance through a glass column (or tube) that is packed with some kind of filter. A chemical sample is placed on top of the column. Some kind of solvent is then poured into the top over the chemical sample. Gravity draws the solvent downwards, and different compounds or components of the mixture travel through the solid at different rates and are separated. The separated compounds are collected in test tubes placed below the glass column. These are standard techniques used to separate compounds. They are also the standard methods used to separate diastereomers, because diastereomers usually have different chemical properties and separate well using these methods.

Enantiomers – stereoisomers that are mirror images of each other – require a different separation technique because they are so similar. Ganem at 174: 13-25. The best way to separate a mixture of enantiomers is to use other enantiomers. Ganem at 175: 6-8. In essence, this is done by placing a material that is chemically either in the all (R) or all (S) configuration in the column chromatography apparatus. If a solvent containing the opposite configuration is poured through the material, one of the enantiomers will be drawn through the material faster than the other and thus separate. Ganem at 176: 8-22. The same kind of process may be used by means of crystallization techniques.

Other separation methods include spectroscopy, which identifies substances by means of the spectrum emitted or absorbed, and nuclear magnetic resonance (“NMR”), a type of spectroscopy that utilizes the magnetic property of an atom’s nucleus. Laird at 475: 24.

The Court **FINDS** that a person of ordinary skill in the art in 1981 would have known about all of these methods.

#### **5. Mercuric acetate oxidation**

In addition to general separation techniques, of particular importance in this case is a synthetic method of creating compounds called mercuric acetate oxidation. Aventis contests its operability in relation to Example 20 found in the “Schering References,” references for which Lupin claims constitute the prior art in this case. Dr. Laird, Lupin’s expert in synthetic chemistry, explained the mercuric acetate oxidation process. The Court found him highly credible and notes that, even though he was an expert witness for Lupin, he is also currently serving as a consultant for Aventis and has served as an expert witness for Aventis in the past. Laird at 440: 2-24.

Example 20 begins with the compound octahydrocyclopentapyrrole, which is to be oxidized by means of mercuric acetate oxidation in the first step of the Example. Laird at 468: 14-15; 468: 16. Mercuric acetate oxidation uses mercuric acetate to produce a chemical transformation known as an “oxidation reaction.” In the most general sense, what happens in mercuric acetate oxidation is that the oxidizing agent removes the hydrogen from the carbon atom, which produces an iminium salt. Two hydrogen atoms are then removed. Laird at 446: 19-21, 25. This, in short, is the dehydrogenation or oxidation process found in the mercuric acetate oxidation step of Example 20.

Specifically, mercuric acetate is used for the dehydrogenation – the removal of hydrogen atoms – of amines. Laird at 449: 12. Amines are compounds that contain nitrogen as the key atom. Laird at 443: 22-25. As explained by Dr. Laird, who used ammonia as an example, primary amines occur when one of three hydrogen atoms in ammonia is replaced by an organic substituent. Laird at 443-44: 24-2. Secondary amines have two organic substituents bound to the nitrogen atom and

only one hydrogen. In tertiary amines, organic substituents replace all three hydrogen atoms. Id.

In the context of Example 20, the key step of mercuric acetate oxidation is the conversion of the amine to an imine. Laird at 445: 5-8. An imine is a chemical compound that contains a carbon-nitrogen double bond. Laird at 444: 10-16. Thus the conversion from an amine to an imine is essentially a conversion from a single to a double bond. Laird at 444: 18. The key contention between Aventis and Lupin is whether the mercuric acetate oxidation process results in giving the second compound in Example 20 a particular imine. Laird at 470: 9-11.

The procedure for the mercuric acetate oxidation process was first described by Professor Nelson Leonard in a well-known scientific paper published on January 20, 1955. Laird at 449: 10-22; Def.'s Ex. 380. He wrote a series of papers subsequent to this publication about the reaction. Laird at 452: 12-17; see, e.g., Def.'s Ex. 348. Leonard's papers focused on tertiary amines. Laird at 466: 17-18. In the Journal of the Chemical Society in 1959, Professor Bonnett published a paper taking Leonard's oxidation process and applying it to secondary amines. Laird at 466: 13-23; Def.'s Ex. 352. The Court **FINDS** that a person of ordinary skill in the art as of 1981 would have either been aware of these papers on mercuric acetate oxidation or would have known how to access the papers by means of a literature search of the chemical abstracts. See Laird at 451: 1-8.

The Court also **FINDS** that Dr. Leonard's papers provided a specific procedure with how to carry out the mercuric oxidation process. In general, the procedure for this process involves mixing mercuric acetate with solvent and heating it to "reflux" (boiling). Laird at 456: 11-20. A solid precipitate is then formed, which is a good sign, although not a conclusive one, that oxidation has occurred. Laird at 457: 15-19. The precipitate, which is often white, is then separated, with liquid mercury often coming out as a by-product and which must be filtered off. Laird at 457: 22; 458: 3-

4. The product that is left is referred to generally as filtrate, and, in this process, is a yellow liquid. Laird at 458: 10, 14. Pursuant to Leonard's instructions, the white precipitate should then be weighed in order to assess how much oxidation has actually occurred. Laird at 458: 20-25. In the 1950s and 1960s, it was a good way to follow the progress of the oxidation. By the 1980s, other methods such as chromatography and spectroscopic methods could be used to follow how the reaction progressed. Laird at 459: 2-6.

The next step in Leonard's procedure is to add hydrogen sulfide to remove whatever mercuric acetate is left. Laird at 459: 12-14. The result is a yellow solution and a black precipitate of mercuric sulfide, which, according to Leonard, must be filtered off. Laird at 459: 14-17; 450: 3-6, 15-18. The liquid left should not have any mercury in it after this filtering. At this point, the imine is still in the yellow liquid, and the liquid contains organic compounds, the amine starting material, and any by-products that have occurred. Laird at 459: 11-13, 21. Thus another separation step is required. In the 1980s, the standard techniques for isolating an organic compound from the remaining liquid included adding an organic solvent to distill the product, a crystallization process, or chromatography. Laird at 461: 1-8.

With respect to adding an organic solvent, Dr. Laird explained that the extraction occurs by adjusting the acidity or basicity (adjusting the pH) of the aqueous (water) layer. Laird at 460: 24-25; 461: 1-2. According to Dr. Laird, Professor Leonard's paper explains that, by adding base to the yellow liquid, the desired product is released. Laird at 462: 23-24. The result is the product dissolved in organic solvent. Leonard's paper also explains that a chemist knows he has the correct product by evaporating the organic solvent and distilling it carefully. Laird at 463: 9-16. The remaining solid or liquid is then generally analyzed by spectroscopy. Laird at 463: 23-24.

Because mercuric acetate is toxic, an alternative method using a different reagent that

achieves the same result was discovered in the 1960s by Professor Gilbert Stork. Laird at 477: 2:16. Dr. Laird also testified that a person of ordinary skill in the art would know of other alternative ways in which to prepare the compounds used in Example 20. Laird at 480: 18-22.

**B. Background: ACE-Inhibitors Generally**

The drugs discussed in this case, including Ramipril, are all “ACE inhibitors.” ACE stands for “Angiotensin Converting Enzyme.” It is an enzyme in the human body that can bind with a compound known as Angiotensin I to produce Angiotensin II. This conversion increases blood pressure by constricting blood vessels. ACE inhibitors such as Ramipril bind with ACE to prevent this conversion from occurring, and the result is lower blood pressure. There are currently ten ACE inhibitors on the market in the United States. Mosberg at 1491.

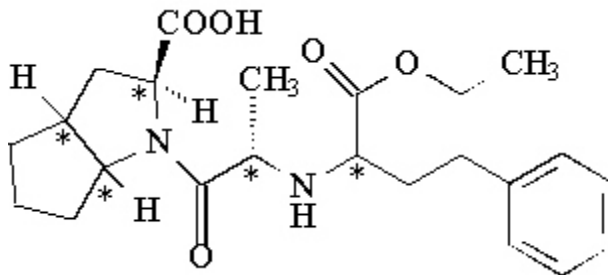
ACE inhibitors began to be developed in the late 1960s, when scientists began studying the venom of the Brazilian Viper because it was known reduce to blood pressure. The venom is made up of several amino acids bound together with all six stereocenters in the (S) configuration. The active compound scientists isolated that reduced blood pressure was known as BPP<sub>5a</sub>. Based on this compound, the pharmaceutical company Squibb succeeded in developing Captopril, the first man-made ACE inhibitor. They did so by cutting off part of the BPP<sub>5a</sub> chain and adding a sulfur atom at the end. The development of Captopril was an early success of “structure-based drug design,” which is the idea that knowing something about the structure of a compound – in this case, a natural compound – allows chemists to design compounds having similar effects. Ganem at 165: 21-23. Captopril has a single five-membered proline ring connected to a side chain with a sulfur atom. It also has two chiral centers, both of which are in the S-configuration.

While Captopril was a tremendous innovation, the presence of the sulfur atom was responsible for allergic reactions in some individuals. In response to this problem, Merck developed

Enalapril, removing the molecule containing the sulfur atom and replacing it with a different molecule. Enalapril has a five-membered proline ring structure. It also has three stereocenters. All of them are in the (S) configuration. Ganem at 181: 3-4. As one of what could be considered the “third-generation” of ACE inhibitors, Ramipril was created by modifying Enalapril. Ramipril differs from Enalapril in that it has an additional ring structure, giving Ramipril two additional chiral centers. Accordingly, Ramipril has a total of five chiral centers. Ramipril’s spatial orientation is discerned by these five chiral centers.

When a molecule, such as Ramipril, has five chiral carbons, there are thirty-two (32) possible configurations of the chiral carbons. In other words, because it has five chiral carbons, Ramipril has five stereocenters with each of the centers determining the molecule's shape. The number one center could be in S, with the rest of the centers in R. Another possibility is that centers one and two could be in S, with centers three, four, and five in R. In this way, thirty-two (32) three-dimensional shapes of the Ramipril molecule are possible ( $2^5 = 32$ ).

The parties agree, and the Court **FINDS**, that the preferred combination of a single molecule of Ramipril has one specific chiral combination, the “S-configuration.” This means that all five chiral centers are in S. This also means that a single Ramipril molecule with the “all S” or “5-S” configuration has a certain shape. The five chiral carbons in a single Ramipril molecule are indicated with an asterisk in the depiction of the molecule below:



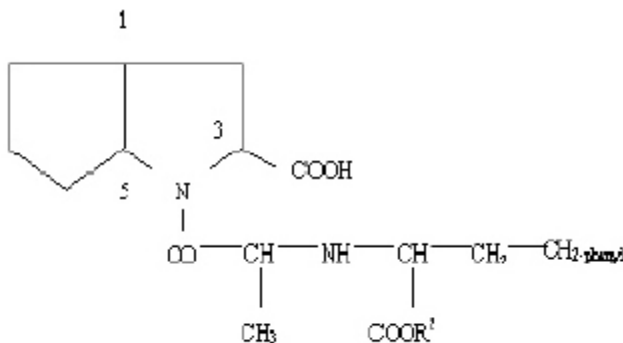
Because the thirty-one (31) other possible versions of Ramipril molecules have the same constituent atoms but are arranged differently based on their chiral carbons, the thirty-one (31) other possible versions of Ramipril are the “stereoisomers” or “isomers” of Ramipril in the 5-S configuration.

### C. The ‘722 Patent

## 1. Ramipril Substantially Free of Other Isomers

Issued on October 29, 1991, the ‘722 patent is entitled “Cis, Endo-2-Azabicyclo [3.3.0]-Octane-3-Carboxylic Acids, A Process for Their Preparation, Agents Containing These Compounds And Their Use.” It covers Ramipril “substantially free of other isomers.” Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are the inventors of the ‘722 patent. The ‘722 patent has the following five claims:

Claim 1: A compound of the formula



or a physiologically acceptable salt thereof, wherein R2 is hydrogen, methyl, ethyl, or benzyl, and wherein hydrogen atoms on the ring carbon atoms in the 1- and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3 - position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration, said

compound or salt being substantially free of other isomers.

Claim 2: A compound or salt as in claim 1 which is N-(1-S-carboethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid or a salt thereof.

Claim 3: A compound or salt as in claim 1 which is N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid or a salt thereof. [Note: this claim is not at issue in this case.]

Claim 4: A hypotensive composition for reducing blood pressure comprising a hypotensively effective amount of a compound or salt as in claim 1 and a pharmaceutically acceptable excipient therefor.

Claim 5: A method for reducing blood pressure in a patient which comprises administering to said patient a hypotensively effective amount of a compound or salt as in claim 1.

Aventis/King has asserted claims 1, 2, 4 and 5 against Lupin. Because all the claims rise or fall with the validity of claim 1, claim 1 has been the parties' and the Court's focus.

#### **D. Chronology of Events Leading to the '722 Patent**

There is little question that Merck's introduction of Enalapril spurred the development of Ramipril. There is also little question that Aventis (previously known as Hoechst)<sup>6</sup> and Schering Corporation were competing with each other to develop Ramipril first. The following chronology thus indicates both Aventis' efforts as well as the Schering Corporation's efforts to develop and patent Ramipril.

The question always in dispute in these cases, apparently, is who invented what and when.

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<sup>6</sup>As the Court reviews the chronology of events leading to the '722 patent, the Court will generally use "Aventis" or "Aventis/Hoechst" for "Hoechst" in an effort to keep the parties straight and avoid confusion.

This case is no exception. Of particular relevance in this case is what Dr. Elizabeth Smith, a chemist employed by Schering Corporation, invented or did not invent. Also of importance is the operability of what is known as “Example 20,” which appears in what Lupin calls the “Schering References,” a series of patents and patent applications that include Application No. 199,886 (the ‘886 application), Application No. 06/258,484 (the ‘484 application), and United States Patent No. 5,348,944 (the ‘944 patent). Ganem at 306-07. Another issue of contention involves United States Patent No. 4,587,258, which Aventis licensed from Schering and, at the least, included a compound that “encompassed” Ramipril. Finally, as several patent applications are at issue, the Court observes that chemistry applications and patents themselves are like puzzles – one compound will be defined in one section, while another section incorporates this compound into its formula. Consequently, in order to understand what a specific example in a patent discloses, it is often necessary to refer back to other portions of the patent based on the example’s instructions. Although, at times, this makes for tedious reading from the Court’s perspective, it is a way for inventors to avoid repeating the same formulas over and over throughout a patent.

### **1. Enalapril**

In June of 1980, Enalapril’s structure was first announced at a scientific conference held in Troy, New York. Ganem at 183: 5-8. On June 25, 1980, Merck’s European patent application for Enalapril was published. Def.’s Ex. 696.

Enalapril’s structure was also published in an article titled “A New Class of Angiotensin-Converting Enzyme Inhibitors” in the prestigious journal Nature in November 1980. Def.’s Ex. 320. Dr. Ganem, Lupin’s expert, whom the Court found credible, testified that one of the key points a person of ordinary skill in the art would take away from the article was that, if the all-S configuration in Enalapril was not followed, “significant potency was lost . . . about a 700-fold difference.”

Ganem at 187: 20-24. More specifically, the article concluded that the “S,S,S for Enalapril was seven hundred times more potent than the S,S,R” version of Enalapril. Ganem at 187-88: 25-1.

Dr. Ganem also testified that the article described how Merck prepared the S,S,S, and S,S,R versions, which are diastereomers, using a type of chromatography and crystallization process. Ganem at 192: 11, 22; 194: 1-8. In addition, he concluded that a person with ordinary skill in the art as of the time the article was published would have been capable of performing these processes. Ganem at 194: 21-22. He also stated that, after looking at Merck’s patent for Enalapril, one with ordinary skill in the art would understand that the (S)-configuration was preferred and that chromatography crystallization worked to obtain a pure compound. Ganem at 207: 1-14.

## **2. Schering – Dr. Smith’s First and Second Disclosures**

Dr. Smith, a chemist for Schering Corporation who was working on ACE-inhibitors, became aware of Enalapril after attending the June 1980 Merck conference and testified, by means of deposition testimony read in open court, it gave her “very interesting information.” Smith at 756: 16. She stated her “first thought was to modify the ring structure . . . and then afterwards work on the side chains.” Smith at 757: 7-9. She also testified: “I think it was stressed enough at the meeting that the (S)-configuration in the side chain was important for the best, you know, the more potent compounds.” Smith at 758: 6-8. On June 20, 1980, a few days after the conference, she prepared a written disclosure in her lab notebooks of the compounds she invented modifying the proline structure in Enalapril. Smith at 761: 16; Def.’s Ex. 1101. Dr. Elijah Gold’s signature appeared beneath Dr. Smith’s on the disclosure. Smith at 761: 23.

Specifically, with respect to a compound identified on page SCH00317 of her lab notebook, Dr. Smith testified that the disclosure encompassed the compound Ramipril. Smith at 762: 19. Regarding the stereochemistry of the compound, she testified:

A: On 3 it is defined in the proline under, under Z, where that carboxylic acid is attached. The stereochemistry is not defined.

Q: Do you have any understanding as to whether the carboxylic acid group in structure 3 [is] in the *endo* position?

A: Carboxylic acid is in 3, it's in the, in the op – and let's see. Endo's – gosh. Endo is down.

Okay. Carboxylic acid is in the same position as it would be in the proline, in the S position.

Smith at 762-63: 20-25, 1-5. She also noted that, on the bottom of page SCH00317, the disclosure “contemplates all possible stereoisomers.” Smith at 766: 4-6.

Q: Okay. Now when you stated, quote, contemplates all possible stereoisomers, end quote, you weren't contemplating that these compounds were going to be together in a substance that had all of the isomers in it, were they?

A: No, we didn't, we didn't intend to have a compound with all of them in there.

Q: Right. Ideally it would have the one most-potent isomer in it?

A: It was hoped that it would be narrowed down. Well, one likes to have a commercial compounds that, you know, have appropriate stereochemistry to give, you know, the maximum activity, and one doesn't want other stereoisomers in it.

Smith at 766-67: 16-25, 1-2.

Dr. Smith made her second disclosure of the “5,5 fused ring system” on August 1, 1980. Id. at 763: 16-19. She testified that the “Z group” in the disclosure corresponded to the side chain for Captopril and that the second side chain would be for Enalapril. Smith at 763-64: 25, 1-2. Dr. Smith also testified that she had an expectation that the compounds she was creating would lower blood pressure better than Enalapril did. Smith at 764: 24-25. She stated that for two years, beginning on June 20, 1980, her primary focus was preparing compounds that satisfied the descriptions in her

disclosures. Smith at 768: 15-19.

### 3. Schering's '886 Application

On October 23, 1980, Schering Corporation filed U.S. Patent Application No. 06/199,886 (the '886 application). Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. The '886 application is a part of a chain of applications leading to Schering's '258 patent and Schering's '944 patent.

Dr. Smith testified that, on page five of the application, the ring structure depicted encompassed 5,5 fused ring systems. Smith at 771: 2-5. Looking at page eleven of the application, Dr. Smith explained that silica gel chromatography, reverse phase chromatography, or fractional crystallization methods were the methods used to separate the "diastereomeric products result[ing] from the synthetic procedures." Smith at 771-72: 16-17, 1-3. Turning to page twelve of the application, Dr. Smith testified that the amino acid structures found in formula one were "preferred in the S configuration," stating this preference related to the fact that "Enalapril had the centers in the S configuration, and it would be important that our compounds have the S configuration in these part structures." Smith at 772: 14-16. She also noted that a third structure on page twelve, referencing R4 and R5, connected to form 5,5 fused ring systems. Smith at 772: 22. Finally, turning to Example 20 of the application on page 22, she testified that the title compound of the Example contained Ramipril. Smith at 773: 5. Example 20 of the '886 application reads as follows:

2 - [ N - ( 1 - C a r b o e t h o x y - 3 - p h e n y l p r o p y l l ) - ( S ) -  
alanyl]octahydrocyclopenta-[b]pyrrole-2(S)-carboxylic acid

A. Substitute octahydrocyclopenta[b]pyrrole (prepared by reduction of 2-ketooctahydrocyclopenta[b]pyrrole in tetrahydrofuran with lithium aluminum hydride) for octahydroisindole in Example 18 A to obtain octahydrocyclopenta[b]pyrrole-2-carboxylic acid.

B. Use ethyl octahydrocyclopenta[b]pyrrole-2-carboxylate (prepared by esterification with the ethanol of the acid prepared as described in paragraph A) in place of ethyl octahydroindole-2-carboxylate in the procedure described in paragraphs B through E of Example 1 to give the title compound.

Def.'s Ex. 15 at LUPRAM 001635. Dr. Smith also stated she “did not synthesize the 5,5 carboxylic acid,” but, at some point, “assemble[d] . . . a compound which contained Ramipril . . . in the 5(S) configuration” as part of a mixture containing other isomers. Smith at 773: 14-16. The Court **FINDS** that the first disclosure of Ramipril as part of a mixture occurred on October 23, 1980, which is the filing date of the ‘886 application. Because both Schering’s ‘258 patent and its ‘944 patent claim priority to the ‘886 application, the Court also **FINDS** that these patents are entitled to an effective filing date of October 23, 1980.

#### 4. Schering – Dr. Smith’s Sample SCH 31925

Dr. Smith testified that, on February 12, 1981, she prepared a compound, referred to as “Sample SCH 31925,” that included the Ramipril molecule, which she recorded in her lab notebooks. Smith at 775: 6-9; 785: 12. According to Dr. Smith, SCH 31925 resulted in two diastereomers, one in the all-(S) configuration and the other with an R at the end of the side chain. She did not separate the mixture. Smith at 889: 17-18; 891: 7-8. Dr. Smith believed she was the first person to make Ramipril in a diastereomeric mixture. Smith at 893: 10-11. Dr. Neustadt confirmed that Dr. Smith made Ramipril in a diastereomeric mixture and did not separate it. Neustadt at 1099: 24; 1118: 12-21. He also testified, however, that “[w]e had an expectation that the material in the (S) configuration would be most potent.” Neustadt at 1122: 7.

Dr. Smith also testified that she used Raney nickel instead of the sodium cyanoborohydride reaction provided for by Example 20. Smith at 824: 4-5. When asked why she did this, she replied: “[o]ne uses sodium cyanoborohydride, and one uses Raney nickel.” Smith at 824: 9-10. She

maintained, however, the SCH 31925 was made by following Example 20 from start to finish, stating “it was made using a different condition[ ] for reductive alkylation.” Smith at 824: 14-15. The Court is not disturbed by Dr. Smith’s admission that she tweaked the process of Example 20. After hearing testimony from various experts – all of whom, it appears, feel free to tweak procedures as they see fit – the Court has no trouble **FINDING** that persons of ordinary skill in the art often tweak experiments based on their understanding of the literature and/or their experience. Accordingly, the Court **FINDS** that, based on the steps outlined by Example 20 in the ‘886 patent and with some tweaking done by one with ordinary skill in the art, Dr. Smith made a diastereomeric mixture of Ramipril, with one part being in the all-(S) configuration (S,S,S,S,S) and the other having an R at the end of the side chain (S,S,S,S,R). The Court has little doubt that the process Dr. Smith used was not an easy one, see infra, but is satisfied that she, indeed, made the compound pursuant to the instructions provided for in Example 20. The Court also **FINDS** that she did not separate the diastereomeric mixture.

The Court also **FINDS** that Aventis concedes that the title of Example 20, “if operable,” would result in “a mixture . . . of at least eight compounds at the end.” Winkler at 1580: 17; 1582:1. See also Mosberg at 1260: 21-1261: 8 (stating that Example 20 describes a compound that “embraces eight stereoisomers”). Dr. Ganem, Lupin’s expert, also agreed that the title compound of Example 20 embraced eight isomers. Ganem at 396: 19-25; 397: 1- 4. The Court notes that all of these conclusions refer only to what the title of Example 20 indicates. Laird at 631: 18-632: 13. The Court is persuaded by Dr. Laird’s testimony, Lupin’s expert, that, while the title encompasses eight isomers, the actual “experimental” that follows instructs that *cis*, *endo* starting compound should be used – and this leads to four products that may then been separating using chromatography methods available to one of ordinary skill in the art. Laird at 630: 17; 631: 12-13. Indeed, Dr.

Mosberg, Aventis' expert, which the Court found somewhat credible even though he refused to directly answer many of the Court's questions and advocated a little too much for the side which was paying for his services, testified that, "even though the title of Example 20 allows for the possibility of eight isomers, for all practical purposes only four could actually be made by following the example" because "the example produces only *cis* bridgehead atoms." Mosberg at 1424: 14-19. Given all of this, and given that Dr. Smith, as a third party and unlike any of the other experts testifying in this case had nothing to gain by testifying one way or the other, the Court has little difficulty finding that Dr. Smith truthfully stated she created a diastereomeric mixture of two compounds of Ramipril, with one part being in the all-(S) configuration (S,S,S,S,S) and the other having an R at the end of the side chain (S,S,S,S,R).

#### **5. Schering's '484 Application**

On April 28, 1981, Schering Corporation filed United States Patent Application No. 06/258,484 (the '484 application). Again, Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. Def.'s Ex. 16. The '484 application is a continuation-in-part of the '866 application. Id. It contains the same Example 20 as the '886 application. Def.'s Ex. 16 at LUPRAM 001300-01. The '484 application is a precursor to Schering's '258 patent and '944 patent.

#### **6. Aventis – Dr. Teetz**

Dr. Volker Teetz, a chemist for Aventis, testified, by means of deposition testimony read into the record, that he synthesized Ramipril on October 28, 1981. Teetz at 966: 1-4. According to Dr. Teetz, the first synthesis he created was a mixture, from which "using [his] knowledge from today," he then isolated an all-(S) configuration of Ramipril as the "main product." Teetz at 967: 13-17. He stated he separated the diastereomeric mixture using column chromatography. Teetz at 974: 22-25.

Dr. Teetz also testified that he was asked to replicate the Schering patent application exactly to see if it would work. He concluded that Example 20 did not work. The Court first observes that Dr. Teetz testified that, when he tried to follow the Schering patent application, he recorded his results in private notebooks, which he destroyed after leaving the company. Teetz at 964: 1-20; 980: 12-18.

Q: So am I to understand that on several occasions you attempted to exactly reproduce the Schering synthesis, but on none of those occasions did you put any entry of those attempts in the official lab notebooks?

A: As far as I can recall, yes.

Q: The private notebooks that you put the attempts to exactly reproduce the Schering synthesis in, were those the same notebooks you destroyed in 1999?

A: Yes. At that point in time in no longer seemed important to me to keep any documentation after 20 or 25 years.

Teetz at 980-81: 19-25, 1-3. After a two-week bench trial in which the Court heard from a variety of experts in chemistry, one thing is clear: keeping private notebooks with important information and then throwing them away is not normal practice for chemists. Dr. Smith's notebooks reveal that she not only carefully dated and recorded her results, but that she also found a witness to sign the appropriate notebook page whenever she created what she thought was an important compound. See supra at II.D.2. While keeping private notebooks might be considered suspect enough, Dr. Teetz also did not even consider returning them to the company he worked for when he left the company but destroyed them instead. These notebooks just happen to contain his attempts to exactly reproduce the Schering synthesis, which he claimed did not work and which was highly contested by Aventis throughout the 1980s before the PTO. The notebooks he kept for his company, in

contrast, were all properly dated and preserved.<sup>7</sup> The Court consequently cannot credit his testimony with respect to Example 20. It also does not accept his testimony that he created Ramipril in the 5(S) configuration “substantially free of other isomers” in 1981 as Aventis contends, given that this phrase was not introduced with respect to Aventis’ patent applications until September 29, 1988 (after the PTO rejected Aventis’ patent applications several times) and that claims 19-23, which became claims 1-5 of the ‘722 patent were not added until October 9, 1984. See infra II.D.13. The Court does **FIND** that Dr. Teetz made a compound that encompassed Ramipril with other isomers, which was included in Aventis’ European patent application and is described immediately below.

#### **7. Aventis’ German Patent Application No. 3143946**

On November 5, 1981, Aventis filed German Patent Application No. 3143946. Pl.’s Ex. 1. Dr. Teetz testified that Example 1 of the patent produced Ramipril in the 5(S) configuration. Teetz at 1036: 7-10, 20-21. He went on to state that the product was “practically pure” and “substantially pure.” Teetz at 1037: 13-20. As noted supra, the Court gives no credence to Dr. Teetz’s testimony, particularly with respect to his contention that, at the outset, he made Ramipril in the 5(S) configuration substantially free of other isomers. The Court is also not convinced that the inventors were even interested in such a compound – the Court notes that Dr. Scholkens, another inventor working with Dr. Teetz, testified that he did not have “any understanding as to when the presence of other isomers in a Ramipril composition can have a material impact on the drug’s therapeutic performance.” Scholkens at 1086: 8-11. Dr. Scholkens also stated that, when he applied for the ‘722 patent, he had no “vision of how isomeric purity could impact the performance of [R]amipril.” Scholkens at 1087: 9-12. Is the Court to believe that Dr. Scholkens, who was working with Dr.

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<sup>7</sup>Negative evidence, unfortunately for Aventis, leads to a positive conclusion.

Teetz, did not know what Dr. Teetz was doing? Who's fooling whom.<sup>8</sup> The Court rejects Dr. Teetz's testimony as to his assertion he made Ramipril in the 5(S) configuration substantially free of other isomers.

There is little question, however, that this application was part of a chain of patent applications that lead to the '722 patent. The Court **FINDS** that the '722 patent is entitled to a foreign priority date of November 5, 1981. The Court does not find, however, that this application disclosed "Ramipril in the 5(S) configuration substantially free of other isomers." The Court notes that the 5(S) configuration apparently was not claimed until October 9, 1984, when PTO noted that Aventis "now claim[ed] the *cis* compound exclusively," see Def.'s Ex. 100 at LUPRAM 000179-80, and that the phrase "substantially free of other isomers" was not introduced with respect to Aventis' patent applications until September 29, 1988 (after the PTO rejected Aventis' patent applications several times).

#### **8. Schering's "Neustadt Application"**

On June 5, 1982, Schering filed European Patent Application No. 50,800 (the "Neustadt Application"). Again, Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. This patent application also contains the Example 20 found in Schering's '886 application. Def.'s Ex. 14 at LUPRAM 001865.

#### **9. Aventis' '757 Application**

On November 3, 1982, Aventis filed U.S. Patent Application No. 06/438,757 (the '757 application). Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens were listed as the inventors. Def.'s Ex. 100. The '757 application is a precursor to Aventis' '722 patent.

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<sup>8</sup>Not me.

#### **10. Aventis' '081 Application**

On March 21, 1983, Aventis filed U.S. Patent Application No. 06/477,081 (the '081 application) as a continuation-in-part of the '757 application. Again, Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens were listed as the inventors. Def.'s Ex. 100. The '081 application is a precursor to Aventis' '722 patent.

#### **11. PTO Office and Advisory Actions**

On April 6, 1984, the PTO rejected claims 1-10, 16, 17 (claims 11-15 were withdrawn) of Aventis' '757 application as "being unpatentable over [Schering's] Neustadt European 50,800" (the Neudstadt patent). Def.'s Ex. 100 at LUPRAM 89-90. The Examiner stated:

Note particularly compounds on pp. 95-96 – per-hydropenta-pyrrole and the process of claim 10(e). The teachings of Neustadt encompass compounds claimed herein and are of common use with those claimed herein. Hence, claimed invention must be deemed prima facie obvious over Neustadt.

Id. at LUPRAM 90.

On May 2, 1984, the PTO rejected claims 1-8, 10, 11, and 18 of Aventis' '081 application (claims 9, 12-17 were withdrawn). The claims were rejected under 35 U.S.C. § 112 for failing to describe in clear terms to enable a person of ordinary skill in the art to make the compounds; under 35 U.S.C. § 103 for being obvious with respect to Schering's Neustadt patent; and under 35 U.S.C. § 103 for being obvious under the teachings of two other patents not involved in this case, the "Hoefle" and "Harris" patents. Id. at LUPRAM 000158-160.

#### **12. Schering's '390 Application**

On July 30, 1984, Schering filed U.S. Patent Application No. 635,390, which eventually issues into U.S. Patent No. 4,587,258 (the '258 patent). It is a continuation-in-part of the '484 application.

### 13. PTO Action

On October 9, 1984, in response to the May 2, 1984 action rejecting its claims, Aventis filed an Amendment to its '081 application, cancelling claims 1-18 and adding claims 19-23. Id. at LUPRAM 000163. Claims 19-23 ultimately become, with some modifications, claims 1-5 of the '722 patent. Aventis also enclosed a Declaration from Dr. Bernward Scholkens, one of the inventors listed on the '081 application, to contest the Examiner's rejection based on obviousness. Id. at LUPRAM 000169. In his Declaration, Dr. Scholkens indicated that the invention in the '081 patent had an ACE-inhibiting activity about three times greater than Enalapril when given to dogs through intravenous injection and consequently was "far superior." Pl.'s Ex. 280 at A000115; Scholkens at 1081: 18-22 (emphasis added). This, according to Aventis' amendment, was a "surprising and unexpected" result. Def.'s Ex. 100 at LUPRAM 000169.

Although not included in his Declaration, Dr. Scholkens, however, testified in this case that Ramipril and Enalapril were "approximately equipotent" after intraduodenal administration. Scholkens at 1082: 1. When asked why he did not include the information about the results from intraduodenal administration as opposed to only including the results from intravenous administration in his Declaration, Dr. Scholkens stated "the declaration is not a scientific paper." Scholkens at 1085: 21.

Q: What does that have anything to do with it?

A: I think there are clear-cut rules for a scientific paper because it's written for scientists, and here we are talking for a document which is, as you said, not for scientists but for the Patent Office.

Q: You don't think a patent officer might not get confused that when you're saying that Compound 4 [Ramipril] is far superior to Compound 1 [Enalapril] they might conclude that you're extrapolating that conclusion to all species or all methods of administration?

A: I'm not the patent officer, and I have to rely on his judgment.

Scholkens at 1085: 22-25; 1086: 1-6.

On November 8, 1984, Aventis filed a Supplemental Amendment, which amended Claim 19 by adding a new formula and including declarations by Dr. Urbach and Dr. Paulus. Def.'s Ex. 100 at LUPRAM 000176-000177.

On December 18, 1984, the PTO rejected claims 19-23 of Aventis' '081 application. With respect to its obviousness determination regarding two other patents not involved in this case, the "Hoefle" and "Harris" patents, the PTO withdrew its determination based on Dr. Scholkens declaration. Def.'s Ex. 100 at LUPRAM 000179. The PTO nevertheless maintained, however, its determination of obviousness with respect to Schering's Neustadt application. The Examiner also stated:

Applicant now claims the *cis* compound exclusively. That compound is not taught in the first priority document. Since the claims as now drawn claims, but the earliest priority document does not disclose, the *cis* isomer, applicant must rely on the later priority document. Hence, this rejection is maintained for reasons of record. Neustadt at p. 23 indicates existence of enantiomers and diastereomers and means of separation. See also p. 26 where the *cis* project is specifically mentioned.

Def.'s Ex. 100 at LUPRAM 000179-180.

On March 15, 1985, Aventis filed a Request for Reconsideration of the Examiner's decision to reject claims 19-23 of the '081 application. Def.'s Ex. 100 at LUPRAM 000182. On April 17, 1985, the Examiner issued an Advisory Action stating the request did not overcome the obviousness rejection. Id. at LUPRAM 000184. On June 3, 1985, Aventis filed another Request for Reconsideration because it "fail[ed] to take into consideration the Paulus and Urbach Declarations filed with the Supplemental Amendment of November 8, 1984 establishing a stereochemical difference between the claimed compounds and those of Neustadt." Def.'s Ex. 100 at LUPRAM

000187-188. Aventis included with its Request further declarations from Dr. Urbach and Dr. Paulus, urging that “the *cis*, endo form of the compounds of the invention and their distinction over the Neustadt reference of record [had been] established.” Id. at LUPRAM 000188, 190.

On July 2, 1985, Aventis appealed the Examiner’s December 18, 1984 decision. Def.’s Ex. 100 at LUPRAM 000192. On July 22, 1985, the Examiner again issued an Advisory Action rejecting claims 19-23. Def.’s Ex. 100 at LUPRAM 000193.

#### **14. Aventis’ ‘284 Application**

On November 19, 1985, Aventis filed U.S. Patent Application No. 06/799,284 (the ‘284 application), which is a continuation of the ‘081 application. Pl.’s Ex. 4. Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id.

#### **15. PTO Action**

On March 20, 1986, the Patent Examiner rejected claims 19-23 of Aventis’ ‘284 application. Def.’s Ex. 100 at LUPRAM 000210. Specifically, the Examiner found the claims “anticipated by Gold/Neustadt,” explaining that “Neustadt is parent application to Gold.” Id. at LUPRAM 000211.

#### **16. Schering’s ‘258 Patent**

On May 6, 1986, Schering’s Patent No. 4,587,258 (the ‘258 patent or “Gold patent”) issued. Elijah Gold, Bernard Neustadt, and Elizabeth Smith are listed as inventors of the patent. Def.’s Ex. 306. The ‘258 patent is a continuation-in-part of the ‘484 application, which was a continuation-in-part of the ‘649 application, which was a continuation-in-part of the ‘886 application. The Court **FINDS** that the ‘258 patent is entitled to the effective filing date of the ‘886 application, which is October 23, 1980.

The ‘258 patent did not have an Example 20; rather, the title of Example 3 in the ‘258 patent indicated that, by following the example indicated, some measurable amount of Ramipril in the 5(S)

configuration was made. Smith at 808: 16-23.<sup>9</sup> Dr. Smith also testified that the Example 20 preparation set forth in the '484 application corresponded to the process set forth in the '258 patent in Example 1, part A. Smith at 806: 9-18.

In addition, Dr. Smith testified that claims 1, 2, 3, 5 and 6 of the '258 patent involved Ramipril. Id. at 810-13. Claim 1, according to Dr. Smith, allowed for "a lot of variations at R1, R3, and R6" that are "one part of a family of compounds." Id. at 812: 9-12. It encompassed Ramipril "with the appropriate stereochemistry." Id. at 810: 20. With respect to Claim 2, she testified:

Q: . . . And, similarly, does the compound description that's presented in Claim 2 of the '258 patent, does this description also encompass the compound ramipril?

A: Yes.

Q: And based on the description of the material as being a cis, endo isomer, would that indicate that within the ring structure itself the stereoconfiguration would be S,S,S?

A: They are all hydrogens on the same side.

Q: And since the carboxylic isomer is S would that also mean that the stereoconfiguration of the two carbons at the ring fusion would also have to be S?

A: Yes.

Smith at 810: 21-24; 811: 1-7. Dr. Smith then explained that claim 3 corresponded to Ramipril. Smith at 811: 13. Claim 5 was the diacid version of Ramipril, which, according to Dr. Smith, refers to the fact that Ramipril gets converted to diacid when it is ingested. Smith at 811: 18-23. Claim 6 describes the compound Ramipril as a hydrochloride salt. Smith at 811: 9-10. Dr. Smith also testified that compound SCH 31925 and the compounds set forth in the '258 patent would lower

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<sup>9</sup>The title of Example 3 is 1-[N-(1(R,S)-Carboethoxy-3-Phenylpropyl)-(S)-Alanyl]-Cis, Endo-Octahydrocyclopenta[b]pyrrole-2(S)-Carboxylic Acid. Def.'s Ex. 306 at A 053262.

blood pressure in the same way. Smith at 814: 3-8. The Court **FINDS** that the ‘258 patent discloses the same mixture as SCH 31925, which was a diastereomeric version of Ramipril, with one part being in the all-(S) configuration and the other having an R at the end of the side chain (S,S,S,S,R).

#### **17. The Taylor, Becker, Barton and Urbach Declarations**

On September 18, 1986, Aventis filed the Declaration of Dr. Edward Taylor, an expert employed by Aventis to repeat the synthesis of the title compound as described in Example 20 of the Neustadt application, with the PTO. Id. at LUPRAM 000215-16. Dr. Taylor concluded that the compound could not be made according to the procedure described in Example 20. Id. at LUPRAM 000216.

On November 18, 1986, Aventis filed the Declaration of Sir Derek Barton, an expert employed by Aventis to repeat Example 20 in the Neustadt Application, with the PTO. Id. at LUPRAM 000232. He also concluded that Example 20 was not operable. Id. Aventis also filed the Declaration of Dr. Becker, who concluded that Ramipril with a mixture of stereoisomers would result from Example 20 of the ‘944 patent if made in a different way from the teaching of Example 20. Pl.’s Ex. 299; Mosberg at 1366: 17-23.

The parties’ experts also testified as to whether Example 20 was operable. Dr. Mosberg, an expert for Aventis who repeatedly said Example 20 did not work, notably was not able to give his opinion on whether a person of ordinary skill in the art having an understanding of the prior literature would have been able to follow Example 20. Mosberg at 1366: 1-23. Dr. Winkler, an expert for Aventis, whom the Court found credible until he refused to interpret the difference in blips on a nuclear magnetic resonance printout obvious even to the Court because such interpretation would not have been advantageous for Aventis, see Winkler at 1591-1600, also stated that Example 20 did not work. Dr. Winkler, in addition, only provided testimony with respect to Dr. Crimmins, who

testified in litigation between Aventis and another generic company in 2003 about the operability of Example 20. Dr. Crimmins did not testify, by means of deposition or otherwise, in this case.

Dr. Laird, for Lupin, testified that Example 20 was operable and pointed out problems with the declarations Aventis' experts submitted stating otherwise. With respect to Dr. Barton's declaration, see Def.'s Ex. 657, Dr. Laird testified that the declaration indicated that Dr. Barton carried out the mercuric acetate oxidation process only once. Laird at 485: 10-12. He then testified that a person of ordinary skill in the art would "hardly ever" do just one experiment; rather, when a reaction is described in the literature, a person of ordinary skill would assume the author's honesty as well as assume he performed the experiment incorrectly or the quality of his reagents were at issue. Laird at 486: 21-26; 487: 1-2. Moreover, Dr. Laird pointed out that Dr. Barton diverged from Leonard's process in several respects. First, after the white precipitate is formed and filtered, he added sodium sulfide instead of hydrogen sulfide, although Dr. Laird noted this did not alter the overall process. Laird at 489: 15-16; see also supra II.D.5 for a description of Leonard's process. Second, instead of following Leonard's distillation of product procedure, Dr. Barton added benzene and boiled out the water. Laird at 490: 1-5. This resulted in a benzene solution that he then boiled off, which left very little product. Dr. Barton also did not characterize what this resulting product was. Laird at 492: 21-23. Thus, from Dr. Barton's data, it is unknown whether the oxidation he conducted made the imine from the amine. Laird at 504: 20-24. Accordingly, the Court **FINDS** that Dr. Barton's declaration does not show that Example 20 does not work, but the Court **FINDS** that Example 20 could work by a chemist with ordinary skill in the art.

With respect to Dr. Taylor's declaration, see Def.'s Ex. 201, Dr. Laird testified that, again, only one mercuric acetate oxidation on the starting material in Example 20 – octahydrocyclopentapyrrole – was carried out. Laird at 525: 15-18. Moreover, Dr. Laird testified

that the declaration indicated that the experiment was not conducted very well. Laird at 525: 22-24. Dr. Laird first related that Dr. Taylor began by following the procedure outlined in Example 20 – mixing the starting material and mercuric acetate in ten percent acetic acid solution and heating under reflux (boiling). Laird at 526: 17-19. Dr. Taylor reported a yellow solution and a precipitate forming within two hours. Laird at 526: 20-21. He then refluxed for 20 hours and extracted the yellow water solution with a solvent. Laird at 526: 23-25. However, after obtaining the organic solvent layer, which was dried and evaporated, the remaining yellow aqueous layer was not analyzed. In Dr. Laird’s opinion, the aqueous layer should have been analyzed because the imine product, if formed, would have been found there. Laird at 527: 5-12. Dr. Laird explained that, because the water layer is acidic,

What he should have done was to basify the water layer to make it basic and then extract it, and that’s when you would get the imine form. That’s the teaching of the Leonard papers, the Bonnet [paper]. . . that you have to basify to get the product to come into the organic layer.

So it’s not surprising he didn’t get any yield . . . .

Laird at 527: 20-25. Dr. Laird then pointed to a paper by Professor Leonard describing mercuric acetate oxidations, see Def.’s Ex. 349, which describes how, when Professor Leonard did what Dr. Taylor did, no yield occurs. Laird at 529: 12-13. However, when the aqueous layer is basified, the paper shows a thirty-four percent yield of the desired product. Laird at 520: 16-17. The Court **FINDS** that Dr. Taylor’s declaration does not show that Example 20 does not work.

On November 14, 1986, Aventis filed with the PTO the declaration of Dr. Reinhard Becker. Pl.’s Ex. 299; Def.’s Ex. 100 at LUPRAM 000242. According to Dr. Mosberg, Aventis’ expert witness, Dr. Becker compared Ramipril with a mixture of stereoisomers that would result from Example 20, “if Example 20 were operable,” and Ramipril in the 5(S) configuration “substantially

free of other isomers” in Aventis’ ‘284 application. Mosberg at 1366: 17-19; 1368: 5-8. Before proceeding further, the Court is compelled to make the following observations about Dr. Mosberg’s testimony. First, when Dr. Mosberg made this statement, the Court asked him how Dr. Becker could compare the two compounds if Example 20 wasn’t operable. Dr. Mosberg replied that the compound was made “a different way.” Mosberg at 1366: 22. The exchange proceeded with Dr. Mosberg not committing to an opinion as to whether one with ordinary skill in the art would have known how to make the compound understanding what the prior literature was, and the Court is inclined to believe he did not do so because it would have been adverse to Aventis. Mosberg at 1367: 22-23. This exchange only bolsters this Court’s finding that one of ordinary skill in the art with an understanding of the prior literature would have been able to make Example 20, just as Dr. Becker was able to do so.

Second, the Court observes that Dr. Becker’s Declaration says nothing about being “substantially free of other isomers.” Dr. Mosberg says the compound compared is “substantially free” because the application at issue ultimately “resulted in the ‘722 patent, so that means Compound A, [R]amipril, made by that process is substantially free of other isomers.” Mosberg at 1368: 5-8. This kind of circular logic ran throughout this litigation. Many times, Plaintiffs’ argument appeared to be that, because the ‘722 patent included the phrase “substantially free of other isomers,” then all the prior art and any testing or commercial success related to Ramipril necessarily related to the product being “substantially free of other isomers,” which is not true.

In any event, Dr. Mosberg testified that Dr. Becker’s results showed that “[R]amipril substantially free of other isomers [Sample A] is about three times more potent than the mixture of stereoisomers that would result from [E]xample 20 [Sample D] and that the onset of action is also quicker.” Mosberg at 1368: 11-14. He also testified that one of ordinary skill in the art would not

have that expectation. Mosberg at 1368: 20.

On cross-examination, however, Dr. Mosberg noted that the amount of 5(S) isomer in the Sample D – the “mixture sample” – was between a quarter to a third. Mosberg at 1406: 10-11. He also agreed that Sample A – the 5(S) compound substantially free of other isomers – was “three times as concentrated . . . in [R]amipril” as Sample D. Mosberg at 1406: 12-14. The following exchange then occurred:

Q: So why is it surprising to a person learned in the art that when you make a Ramipril sample that’s three times more concentrated than another one, you get a potency reading that’s three times as high?

A: Because one of ordinary skill in the art at this time would have no expectation of the activity of the other isomers, the other three stereoisomers in the mixture would have. I mean from today, from hindsight, it’s very clear that that is what you would expect. But not until you actually have looked individually at all the isomers could you have that expectation.

The Court: So it really, what you’re saying, am I to understand, that it depends on the dosage? You take 10 milligrams of something and you take 20 milligrams of something, 20 milligrams is more potent than 10?

A: I think that is generally true. I don’t know it’s always true.

The Court: . . . And what I want to question is if it were 30 milligrams versus 10, would you expect three times the potency generally? Not in this.

A: Generally if you haven’t already maxed out the potency as a lower dose, then you would expect the potency to increase. It’s not linear.

The Court: Well, ACE inhibitors, do doctors generally give greater amounts of milligrams in their tablets to people who have higher blood pressure?

A: I can’t speak as an expert, but I think as a lay person, yes, if a lower dose isn’t effective, a doctor would give a higher dose.

The Court: Why?

A: The understanding that more of the drug will have more of the effect.

Mosberg at 1406: 18-25; 1407: 1-25. Dr. Mosberg continued by saying that the Declaration itself demonstrated that, if Sample D – the mixture – was given in a 30 milligram dose, it would lower blood pressure as well as Sample A – the substantially free – in a 10 milligram dose. Mosberg at 1408: 6-9. The Court **FINDS** that, according to Dr. Mosberg, if Sample D had three times the concentration of the 5(S) isomer, it would perform the same as Sample A. Put simply, the more 5(S) isomer you have, the more potent the compound is. Given this obvious outcome, the Court therefore does not agree with Aventis that Dr. Becker showed that Ramipril in the 5(S) configuration substantially free of other isomers showed an “unexpected result” compared to Ramipril made from Example 20. The Court, however, is not convinced – by clear and convincing evidence – that Ramipril in the 5(S) configuration substantially free of other isomers is meaningless, as the parties agree that the 5(S) configuration is preferred.

On November 14, 1986, Dr. Hansjorg Urbach submitted a Declaration stating that the title compound of Example 20 in the Neustadt Application did not work. Def.’s Ex. 100 at LUPRAM 000249. Dr. Laird, Lupin’s expert, reviewed the detailed experimental that Dr. Urbach presented in his declaration. Laird at 548: 19. He testified that Dr. Urbach stated that he obtained a mixture of Ramipril in the 5(S) configuration and its stereoisomer, the S,S,S,S,R compound, in a 65 to 35 ratio. Laird at 550: 15-18; see also Def.’s Ex. 17 at LUPRAM 000557 (Urbach Declaration). Although the title compound of Example 20, which has an “ethyl ester” and thus would require ethanol to be used as a solvent rather than methanol, Dr. Urbach, however, used a “mixture of methanol and ethanol.” Laird at 558: 6-12. Dr. Laird noted that Example 1-E, which followed from Example 20, instructs that ethanol *or* methanol may be used, depending on the ester desired, but it does not instruct that a mixture be used. Laird at 559: 1-4. According to Dr. Laird, Dr. Urbach thus

made Ramipril as part of a mixture following Example 20. Laird at 560: 22. Dr. Laird also testified that, if the experiment was done correctly using only ethanol, it would have resulted in Ramipril and the ethyl ester, which would have been separable by chromatography. Laird at 562: 1-3.

On cross-examination, Dr. Laird agreed that Dr. Urbach stated in his declaration that he planned to discuss the “theoretical question of what would have been the result of Example 20 B,” but went on to note that Dr. Urbach nevertheless went on to do it. Laird at 623: 5-8. It was then pointed out that Dr. Urbach did not perform Example 20A because he made a substitution. Laird at 624-25. Again, this only reinforces the Court’s finding that chemists having ordinary skill in the art tweak as they make chemical compounds to achieve the result they seek. In other words, a good chemist learned in the art, if he wants to make the compound can, and, if he doesn’t, he won’t.

### **19. PTO Action**

On December 9, 1986, the Examiner rejected claims 19-23 of Aventis’ ‘284 application for being “anticipated by Gold U.S. 4,587,258” (the ‘258 patent). Id. at LUPRAM 000269-270. The Examiner noted that the Aventis urged that “Gold is not enabling,” but observed that “a U.S. patent is presumed valid.” Id. at LUPRAM 000271.<sup>10</sup> The Examiner invited the parties to participate in an interference proceeding.<sup>11</sup> Id.

On December 12, 1986, the Examiner issued a Supplemental Response entering the

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<sup>10</sup>Although Aventis told this Court on numerous occasions that it was not rehashing arguments made before the PTO about the enablement of Example 20 in the Schering References and the enablement of the ‘258 patent, the Court sees it otherwise. The PTO heard all of the arguments the Court heard and found that Schering invented Ramipril, at least as part of a mixture, first.

<sup>11</sup>“Section 135 of the United States Code, Title 35, governs patent interference proceedings, which are designed to determine whether two patent applications (or a patent application and an issued patent) are drawn to the ‘same patentable invention’ and, if so, which of the competing parties was first to invent the duplicative subject matter.” Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington, 334 F.3d 1264, 1267 (Fed. Cir. 2003).

Declarations of Dr. Becker, Dr. Taylor, and Dr. Burton. Id. at LUPRAM 000275. The Examiner maintained his rejections, stating:

The declarations are not persuasive of inoperability since no averment is seen that declarants did not know of other means to make the named compounds of Gold . . . . More is required that simply showing Gold's compounds can not [sic] be made by the process disclosed by Gold. There is a burden on the junior to prove by a preponderance of the evidence the taught process could not have been made operative by persons of ordinary skill in the art with the teaching of the disclosure before him.

Id. (internal citations omitted).

### **19. Schering/Aventis License Agreement**

On December 15, 1986, Aventis/Hoeschst and Schering Corporation entered into an agreement in which Schering granted Aventis a license under Schering's patent rights to produce pharmaceutical products containing Ramipril under the condition that Schering would be paid \$500,000 upon execution of the agreement, \$500,000 upon FDA approval to market the licensed product, and five percent of Aventis' net sales of Ramipril.<sup>12</sup> Pl.'s Ex. 317 at SCH 001463, SCH 001465. The term "licensed compounds" was defined to mean the following in Section 1.1.:

2-[N-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S, 3S, 5S)-2-oxabicyclo [3,3,0]octane-3-carboxylic Acid (Ramipril) and 2-[N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl]-(1S, 3S, 5S)-2-azabicyclo[3.3.0]octane-3-carboxylic Acid (Ramiprilat) including their salts, hydrates and solvates.

Id. at SCH 0001461. Schering's Neustadt Patent (50,800), the '484 application, and the '258 patent were among the patents listed in Appendix A to be licensed by Aventis. Id. at SCH 001475.

### **20. PTO Action**

On May 19, 1987, Aventis filed a Request for Reconsideration of the Examiner's rejection

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<sup>12</sup>The payments of \$500,000 were to be credited against the royalties Schering received. Pl.'s Ex. 317 at SCH 001464.

of claims 19-23 of the '284 patent. Def.'s Ex. 100 at LUPRAM 000278. Aventis specifically pointed out that the compounds of each of claims 19-23 "characteristically have five chiral centers, each of which is in the S-configuration." Id. at LUPRAM 000280. Aventis also stated:

Compounds having this substituted ring structure and an appended sidechain on the ring nitrogen atom are shown in the Gold '258 patent and are claimed in Claims 3-6 and 131-6, for instance. These Gold compounds, since they are cis, endo and have both chiral centers in the sidechain in the S-configuration, are also S,S,S,S,S compounds. Support for compounds of these specific steric configuration is to be found in Examples 3, 5, and 10 of the Gold patent with the synthesis of the compounds being supported by Examples 1 and 2.

However, the Examiner will search in vain for a similar disclosure of these specific S,S,S,S,S compounds in any of the prior applications of Gold et al. indicated as being predecessor applications.

Id. at LUPRAM 000280-281. On May 27, 1987, Aventis communicated to the Examiner that they wanted an interference proceeding declared with respect to the '258 patent on "specific claimed isomers." Id. at LUPRAM 000285.

## **21. Interference Proceeding**

On January 12, 1988, the Board of Patent Appeals and Interferences declared Interference No. 101,833 between Elijah Gold, Bernard Neustadt, and Elizabeth Smith, inventors of the '258 patent, and Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens, inventors of the '284 application.

On June 30, 1988, Dr. Jerrold Meinwald made a declaration stating that Example 20 worked and refuting the declarations made by Dr. Taylor and Dr. Barton that it did not. Def.'s Ex. 659A at SCH-001587, SCH-001595. Dr. Meinwald stated that Example 20 created yields of 32 to 35 percent of the desired product.<sup>13</sup> Def.'s Ex. 659A at SCH-001591. According to Dr. Laird, Dr.

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<sup>13</sup>Dr. Meinwald also referred to Example 5 of the Neustadt application, which is the same thing as Example 20. Laird at 556: 13-15.

Meinwald got a mixture of isomers. Laird at 628: 17. Dr. Meinwald then obtained an NMR spectra of the *endo* and *exo* isomers, which, in Dr. Laird's view, indicated that he separated them. Laird at 630: 6-8.

On September 29, 1988, Aventis submitted an Amendment to the '284 application adding the phrase "said compound or salt being substantially free of other isomers" to Claim 24. Def.'s Ex. 38 at A 034383-84.

September 30, 1988 was an eventful day for both Aventis and Schering. First, Aventis filed a Concession of Priority "as to the present broad Count of [the] interference." Pl.'s Ex. 373 at SCH 001453. The Concession indicated that Aventis

intend[ed] to pursue, in ex parte prosecution, claims directed to a narrower invention, i.e., the compounds of claims 19 to 23 of the involved Teetz application which are substantially free of other isomers, on the basis that this narrower invention represents a separate patentable invention over the present broad Count of this interference. Further, Teetz [did] not concede priority with regard to this narrower invention.

Id. at 373 at SCH 001453-54. Second, Schering filed a Disclaimer disclaiming Claims 3-6 of the '258 patent. Pl.'s Ex. 314. Third, the license agreement between Schering and Aventis was amended giving Schering a 2.5% royalty for the Schering patents. Pl.'s Ex. 319 at SCH 001484.

On October 12, 1988, the Board of Patent Appeals and Interferences terminated the interference based on Aventis' Concession of Priority.

## **22. NDA Submitted for Altace**

On November 2, 1988, by virtue of the license agreement of the '258 patent with Schering, Aventis submitted a New Drug Application with the FDA for **ALTACE**, Aventis' marketing name for Ramipril. Pl.'s Ex. 384 at 601. On November 17, 1988, FDA acknowledged receipt of the applications and assigned it NDA No. 19-901. Id. at 635.

### 23. Aventis' '513 Application

On January 12, 1989, Aventis filed Patent Application No. 07/296,513 (the '513 Application), a continuation of the '284 application. Def.'s Ex. 100 at LUPRAM 000398. Volker Teetz, Rolf Geiger, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id.

On April 7, 1989, Aventis submitted a Preliminary Amendment to the '513 Application. Id. at LUPRAM 000453. In the amendment, Aventis asked to cancel Claims 1-18 and add Claims 19-23. Id. at LUPRAM 000455. Claim 19 now included the phrase "substantially free of other isomers." Id.

In addition, to "further support their claim that the claimed compounds are patentable," Aventis attached several declarations stating that Example 20 of the Neustadt Application was not operable, some new and some of which had been submitted with respect to other patents and applications. See id. at LUPRAM 00453-474. One of the declarations submitted on April 7, 1989 was by Dr. Teetz, who stated that Example 20 did not work. Def.'s Ex. 661. Dr. Laird pointed out that, while Dr. Teetz says he repeated Example 20, he doesn't provide the experimental for that repetition. Laird at 503: 2-5. He also made several modifications which are not mentioned in the preamble of his declaration, but are found in the appendix. Laird at 508: 11-14. First, although Example 20 requires one to start with the compound *cis*, octahydrocyclopentapyrrole, Dr. Teetz started with *cis*, octahydrocyclopentapyrrole hydrochloride. Laird at 503: 9-10. Then, instead of using 10% acetic acid as Example 20 instructs, he changed the amount to 20%. Laird at 505: 6-7. Finally, when he heated the mixture, he only did so for nine hours instead of twenty hours. Laird at 505: 12-13. He ran the experiment for this time even though he stated in his declaration he had followed the procedures outlined in Bonnett's paper, see supra at II.A.5, which instructs heating the mixture under reflux (boiling) for 20 hours. Laird at 513: 5-7.

In addition, after running the experiment, Dr. Teetz reported he got a yield of .05 % of the desired product. Laird at 509: 8. Dr. Laird testified that, although this was a small yield, a person of ordinary skill in the art would not have concluded that the mercuric acetate oxidation process did not work; rather, such a person would conclude it worked but didn't result in a useful yield. Laird at 509: 19. As noted supra, the Court already does not accept Dr. Teetz's credibility based on the fact that he destroyed what he called private notebooks in which he conducted his repetitions of Example 20. Moreover, since there were no dated notebooks for his company, which presumably was paying for his experiments, the Court does not find such testimony credible. It is easy to understand why Aventis/King would not present Dr. Teetz, their chief witness, by live testimony – he apparently does not need his notes to testify with particularity exactly what was done twenty-five years before. The Court also **FINDS** that Dr. Teetz's experiment actually resulted in a small amount of Example 20 and thus his declaration does not show that Example 20 does not work. Moreover, the Court **FINDS** that Dr. Teetz's declaration exemplifies behavior by chemists the Court has observed throughout this case, namely, that chemists, especially chemists of high skill such as the chemists involved here, tweak experiments based on their understanding of the literature, their experience, and their goals.

Additionally, Aventis submitted a Declaration from Dr. Becker dated April 29, 1989 in which he concluded that "Compound X," which was Ramipril in the 5(S)-configuration "substantially free of other isomers," was "far superior" to its stereoisomers "as to their ACE inhibiting activity." Pl.'s Ex. 324 at A 000270. The compounds Dr. Becker compared to Ramipril in the 5(S)-configuration "substantially free of other isomers" included "10 or 11 stereoisomers of [R]amipril, including the four stereoisomers that would result from [E]xample 20 in the Schering patent." Mosberg at 1370: 12-14.

According to Dr. Mosberg, an expert witness for Aventis, “Compound VI,” which had the R,R,S,S,S configuration, was the next most potent compound after Ramipril in the 5(S)-configuration “substantially free of other isomers.” The R,R,S,S,S configuration was one of the stereoisomers that would result from Example 20. Mosberg at 1371: 25; 1372: 1-13. According to Dr. Mosberg, Ramipril in the 5(S)-configuration “substantially free of other isomers” was “about 18 times more potent” than Ramipril in the R,R,S,S,S configuration. Mosberg at 1373: 6-7. The other stereoisomers tested were even less potent. Mosberg at 1373: 11. Dr. Mosberg also testified that the “only difference [between Ramipril in the 5(S)-configuration “substantially free of other isomers” and Ramipril in the R,R,S,S,S configuration] is the Rs and Ss at the bridgehead” portion of the Ramipril molecule. Mosberg at 1373: 14-15. Dr. Mosberg concluded that one of ordinary skill in the art would not have expected these results. Mosberg at 1375: 11. While the Court is not convinced that one of ordinary skill in the art would not have expected these results, the Court does **FIND** that Ramipril in the 5(S) configuration is preferred stereoisomer of Ramipril, as it is about 18 times more potent than Ramipril in the R,R,S,S,S configuration.

In addition, Dr. Mosberg explained that an “excipient” in a pharmaceutical compound serves only as filler and does not add anything to the compound’s activity, *i.e.* excipients are therapeutically inactive. Mosberg at 1413: 5-16. He also testified that, when calculating the amount of a drug present in a product, excipients are excluded from the calculation. Mosberg at 1413: 17-20. With respect to adding an isomer that added nothing therapeutically to the drug, however, Dr. Mosberg would not label such an isomer as an “excipient” but as an “impurity.” Mosberg at 1414: 2-8. Dr. Mosberg was then asked if there was a difference between the blood pressure lowering ability of a sample containing 10 milligrams of only the 5(S)-isomer of Ramipril and a sample containing 10 milligrams of the 5(S)-isomer of Ramipril plus 10 milligrams of a therapeutically inactive

stereoisomer of Ramipril. Mosberg at 1415: 15-19. Dr. Mosberg testified that he “couldn’t say that one would act better than the other to lower blood pressure . . . if all we’re talking about is the therapeutic activity without any regard to possible toxicity or other side effects.” Mosberg at 1417: 8-11. Dr. Mosberg said he had no evidence of toxicity or side effects associated with any of the Ramipril isomers. Mosberg at 1417: 12-13. He also said that it was “possible” that a lot of “off-isomer” could “affect absorption,” although he had no evidence of that in this context. Mosberg at 1420: 17-25-1421: 4-8. Although the 5(S) configuration of Ramipril is clearly preferred, the Court **FINDS** that no evidence was shown of toxicity or side effects associated with any of the other stereoisomers of Ramipril.

Finally, Dr. Mosberg also testified that, looking at the ‘722 patent, there was no data indicating that Ramipril in the 5(S)-configuration substantially free of other isomers would lower blood pressure any better than a Ramipril sample with other isomers in it. Mosberg at 1427: 7-12. When asked “if the advantage of [R]amipril substantially free of other isomers is that it’s more potent, wouldn’t [he] expect some of that information to make its way into the ‘722 patent,” Dr. Mosberg said he didn’t know what would be expected. Mosberg at 1428: 5-18. After reviewing the ‘722 patent, the Court **FINDS** that there is no data within the patent itself that indicates why the 5(S) configuration “substantially free of other isomers” would be preferred over one not substantially free of other isomers.

### **23. PTO Office Action**

On October 4, 1989, the Examiner rejected claims 19-23 of the ‘513 patent under 35 U.S.C. 102(g). The Examiner stated:

Claims 19-23 are rejected as being unpatentable over the lost count of Interference 101,833, under 35 U.S.C. 102(g). In particular, as stated in the judgment rendered Oct. 12, 1988, applicants are “not entitled to a patent containing claims 19-23 corresponding to the

count.” Although it is applicants’ contention that the claims to the specific isomer represent a separate patentable invention over the broad count of the interference (Remarks of April 7, 1989, page 8), this is inconsistent with the judgment rendered in the interference. The isomers as well as the genus were included in the interference as evidenced by the inclusion of applicants’ claims 19-23, drawn to the isomers, as well as both the genus (claim 1) and the specific isomers (claims 2-23) of Gold [the ‘258 patent] et. al. The term “being substantially free of other isomers” is not considered to be a limitation which distinguishes the instant claims from the claims involved in the interference.

Def.’s Ex. 100 at LUPRAM 000790.

#### **24. Aventis Amends ‘513 Application**

On April 6, 1990, Aventis submitted an Amendment of its ‘513 Application to the PTO. In its amendment, Aventis maintained that the disclosure in the ‘258 patent was not prior art to the ‘513 application and thus the ‘513 Applicants “need only show that claims 19-23 of the present application are patentable over the lost count of Gold.” Id. at LUPRAM 000807-000808. Aventis reasserted its contention that Claims 19-23 were “directed to compounds which are substantially free of other isomers and having five chiral centers in the S-configuration, constitute a separate and patentably distinct invention from the lost count of Gold et. al.” Id. at LUPRAM 000808. Aventis also referred to the Becker Declarations to reargue their position that Claims 19-23 were “unobvious with respect to the isomeric mixtures of the count of Gold et al. by virtue of their unexpectedly superior ACE-inhibiting activity.” Id. at LUPRAM 000810.

#### **25. PTO Action**

On June 21, 1990, the Examiner rejected Claims 19-23 of the ‘513 application under 35 U.S.C. 112 paragraph 1 because “there is no express support for the limitation ‘being substantially free of other isomers’” in the specification. Id. at LUPRAM 000855. The Examiner also found that the “working examples do not indicate the exact purity obtained.” Id. In addition, the Examiner

again rejected the claims as being unpatentable over the lost count of interference 101,833 under 35 U.S.C. 102(g). Id.

## 26. Aventis' '513 Application

On December 24, 1990, Aventis submitted a Declaration by Dr. Urbach clarifying that the “methods of Example I(1)-I(5) lead only to a single compound in which each of the five chirality centers in the compound has the S-configuration, being substantially free of other isomers.” Id. at LUPRAM 000868. The methods were then examined in greater detail. Id. at LUPRAM 000869-878.

## 27. Altace Approved by the FDA

On January 28, 1991, Altace under the '258 patent was approved by the FDA to be sold in the United States. Pl's Ex. 384 at 601. The Court **FINDS** that this approval occurred prior to the issuance of the '722 patent, which claims Ramipril “substantially free of other isomers” and which Plaintiff's counsel emphasized is the Altace product.

The Court: What does substantially free from other isomers do for you?

Mr. Hsing: Is it gives you Altace, this fantastic drug, which is a pure, substantially pure Ramipril. Ramipril *cis endo* 5(S) substantially free from other isomers. That is the Altace product.

The Court: So substantially free from other isomers is absolutely essential for Ramipril?

Mr. Hsing: Yes. . . .

Trans. at 591: 16-24. The Court observes Aventis' emphasis that Altace in the 5(S) configuration is substantially free of other isomers because Aventis' appears to have represented otherwise to the PTO and FDA, as indicated below. See infra II.D. 29, 31.

## 28. Aventis Amends '513 Application Again

On February 1, 1991, Aventis submits a Supplemental Amendment to the ‘513 application, amending claim 24 to correct “an inadvertent error in the structural formula.” Id. at LUPRAM 000897. The Amendment also requested the Examiner to consider Dr. Urbach’s December 1990 Declaration. Id. at LUPRAM 000898.

## **29. Application for Extension of ‘258 Patent Submitted**

On March 27, 1991, Aventis submitted, pursuant to 37 C.F.R. § 1.710, a Letter of Transmittal of Application for Extension of the ‘258 Patent. Pl.’s Ex. 384 at 594. Aventis had the authority to submit this letter because Schering appointed Aventis as agent to submit a patent term extension on its behalf on March 11, 1991. Id. In its letter to the PTO, Aventis stated the following:

- “Approved product is Ramipril [title of drug and chemical formula provided] . . . . Ramipril is the active ingredient of the new drug, Ramipril capsules, which has received FDA approval.” Id. at 596.
- “Ramipril was approved by FDA for commercial marketing . . . on January 28, 1991.” Id. at 597.
- “The sole active ingredient of the approved drug (which is a human drug) is Ramipril as identified above under Paragraph 1 and it has not previously been approved for commercial marketing or use under the [Federal Food, Drug, and Cosmetic Act].” Id.
- “A copy of Statutory Disclaimer under 35 U.S.C. 253(a) filed by Schering Corporation on September 19, 1988 is attached hereto as Exhibit D. Said document disclaims Claims 3 through 6, inclusive, of said Gold et al patent.” Id. at 598.
- “Claim 2 claims a compound according to Claim 1 which is a cis,endo isomer of octahydrocyclopenta[b]pyrrole-2(s)-carboxylic acid. Claim 2 reads directly on Ramipril . . . .” Id. at 599.

The letter concludes by asking for an extension of 632 days for the ‘258 patent based on the fact that the product had been subject to a regulatory review period before its commercial marketing. Id. at 604. Neither the original filing with the FDA nor the subsequent extension requested and obtained related to any patent other than the ‘258 patent.

By licensing the ‘258 patent from Schering and then requesting an extension of the patent, the Court **FINDS** that Aventis conceded that the ‘258 patent contained an enabling disclosure for Ramipril – to such an extent, in fact, that it sought approval to market Altace from the FDA based on the ‘258 patent because the ‘722 patent had not yet been issued. Indeed, in its letter to the PTO for an extension of the ‘258 patent, Aventis states that “[t]he sole active ingredient” was found in the formula of Ramipril in the ‘258 patent. *Id.* at 597. The Court consequently cannot accept any argument from Aventis that, in spite of these actions on its part, the examples provided in the ‘258 patent did not work and the ‘258 patent is not prior art. Moreover, since 2000, Schering has made more than \$48 million by licensing the ‘258 patent for a 2.5% royalty based on Altace’s net sales. *McSorley*: 1948: 22-25; 1949: 1-15. The Court finds it interesting that Aventis would pay \$48 million to license a patent yet nevertheless maintain that it was not enabled and is not prior art even though they made applications based on Schering’s ‘258 patent.

Interestingly, in its Post-Trial Brief, Aventis now maintains that the “active ingredient in Altace is [R]amipril substantially free of isomers” in spite of its representation to the PTO that Ramipril under the ‘258 patent contained the “sole active ingredient” in Altace. *Pl.’s Post-Trial Br.* at 30. The Court therefore is tempted to find the ‘258 patent contained an enabling disclosure for Ramipril “substantially free of other isomers,” although, based on the record before it, it is apparent to the Court that the ‘258 patent disclosed a compound containing Ramipril but not a separated compound of Ramipril in the 5(S) configuration “substantially free of other isomers.”<sup>14</sup> The Court can only wonder, though, how Ramipril “substantially free of other isomers” makes any difference given Aventis’ representations to the PTO and the FDA that Ramipril not substantially free of other

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<sup>14</sup>Indeed, Lupin concedes that the ‘258 patent describes “a product or substance containing [R]amipril.”

isomers is Altace. Indeed, the Court wonders if Dr. Teetz destroyed his notebooks precisely because he knew Ramipril's purity made no difference, although the Court has no proof to back up its suspicions in this regard one way or the other. The problem for Lupin is that the Court isn't persuaded, by clear and convincing evidence, that Ramipril's isomeric purity doesn't make a difference either. In any event, with all of this said, the Court is not finding that the Ramipril taught in the '258 patent was "substantially free of other isomers," although it notes that Altace was somehow approved by the FDA based on the '258 patent and prior to the issuance of the '722 patent.

### **30. PTO Action**

On April 22, 1991, the Examiner's Interview Summary Record indicates that the Examiner communicated to Aventis that claim 24 of the '513 application "appears to be claiming the same compound free of other isomers as claim 19." Def.'s Ex. 100 at LUPRAM 000899. The Examiner also stated that Aventis agreed to the Examiner's amendment to cancel claim 24. Id.

### **31. Altace Listed in the FDA Orange Book**

In July 1991, Altace is listed in the FDA Orange Book. The Court **FINDS** that this listing occurred prior to the issuance of the '722 patent and was based on the '258 patent. See Pl.'s Ex. 384 at 595-660; Maness at 1665: 3-5.

### **32. '722 Patent Issues**

On October 29, 1991, U.S. Patent No. 5,061,722 issues (the '722 patent) from the '513 application. Pl.'s Ex. 1. Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id. It is listed as a continuation of the '284 application, now abandoned, which was a continuation of the '081 application, now abandoned. The '081 application is listed as a continuation-in-part of the '757 application. Id. It is entitled to a foreign priority date of November 5, 1981 based on Aventis' German Patent Application No.

3143946. The ‘722 patent is entitled to an effective U.S. filing date of November 3, 1982 based on Aventis’ ‘757 application. The Court notes that the 5(S) configuration apparently was not claimed until October 9, 1984, when PTO noted that Aventis “now claim[ed] the *cis* compound exclusively,” see Def.’s Ex. 100 at LUPRAM 000179-80, and that the phrase “substantially free of other isomers” was not introduced with respect to Aventis’ patent applications until September 29, 1988 (after the PTO rejected Aventis’ patent applications several times). Lupin, however, is not contesting the November 3, 1982 filing date by maintaining that “new material” was added, although, arguably, it could. The Court **FINDS** that the ‘722 patent is drawn to Ramipril in the 5(S) configuration “substantially free of other isomers.”

### **33. ‘258 Patent Term Extension Granted**

On December 30, 1991, the PTO extended the term of the ‘258 patent by 632 days. Pl’s Ex. 384 at 662.

### **34. ‘944 Patent Issues**

On September 20, 1994, Schering’s ‘944 patent issues. Def.’s Exhibit 301. It is a continuation of the ‘484 application, abandoned, which was a continuation-in-part of the ‘649 application, now abandoned, which itself was a continuation-in-part of the ‘886 application, now abandoned. Id. It contains Example 20.

### **35. The HOPE Study**

On January 20, 2000, The New England Journal of Medicine described the results of a study called “The Heart Outcomes Prevention Evaluation Study” (“HOPE Study”). Def.’s Ex. 338. The HOPE Study evaluated the effects of Ramipril in comparison with a placebo in “high-risk” patients having evidence of vascular disease and diabetes but who were not known to have “a low ejection fraction or heart failure.” Id. The HOPE Study concluded that Ramipril “significantly reduces the

rates of death, myocardial infarction, and stroke” in these patients. Id. Dr. Pitt, Aventis’ expert, testified, by means of deposition testimony read into the record, that the study showed an “overall reduction of 22 percent myocardial infarction and stroke” in patients taking Ramipril compared to those taking a placebo and that Ramipril reduces the risk of cardiovascular death by 25 percent. Pitt at 1783: 3:17. On October 4, 2000, the HOPE indication for Altace was approved by the FDA.

The parties do not dispute that the HOPE Study was an excellent study. The Court **FINDS** that the HOPE Study concluded that Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in high-risk patients who had not had heart failure. The Court also **FINDS** that the HOPE Study compared Ramipril to a placebo, and that the HOPE Study methods were not repeated using ACE-inhibitors in the same patient population. Accordingly, the Court cannot find that Ramipril is superior to other ACE-inhibitors in this regard as there are no studies indicating as such.<sup>15</sup> There was also no evidence provided that the HOPE Study indication resulted from Ramipril being “substantially free of other isomers.” The Court therefore cannot make a finding that Ramipril being “substantially free of other isomers” was the cause of the HOPE Study indication, particularly as the Court has seen no evidence as to the therapeutic value of Ramipril – or any ACE-inhibitor for that matter – being “substantially free of other isomers.”

### **36. ‘258 Patent Expires**

On January 27, 2005, the ‘258 patent expired.

#### **E. Altace’s Commercial Success**

The parties stipulated to the following facts in relation to Altace’s commercial success:

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<sup>15</sup>Perinodopril, an ACE-inhibitor with the 5(S) configuration and a 6,5 bicyclic ring, apparently also prevented heart attacks. The patients in that study, however, were from a different population. The Court has no direct evidence in this regard, although there was some indication from Dr. Pitt, Aventis’ witness, and Dr. Wharton, Lupin’s witness, that Perinodopril had a similar indication as Ramipril for preventing heart attacks.

- In December 1998, King paid over \$350 million for an exclusive license to sell Altace in the U.S.
- Wyeth paid King \$75 million for the right to co-promote Altace in the U.S.
- From 1999-2005, gross sales of Altace in the U.S. were as follows:
  - 1999: approximately \$140.6 million.
  - 2000: approximately \$184.2 million.
  - 2001: approximately \$327.4 million.
  - 2002: approximately \$603.2 million.
  - 2003: approximately \$728.1 million.
  - 2004: approximately \$684.1 million.
  - 2005: approximately \$808.2 million.
- From 1999-2005, net sales of Altace in the U.S. were as follows:
  - 1999: approximately \$121.8 million.
  - 2000: approximately \$161.9 million.
  - 2001: approximately \$284.6 million.
  - 2002: approximately \$450.0 million.
  - 2003: approximately \$536.9 million.
  - 2004: approximately \$347.3 million.
  - 2005: approximately \$554.4 million.
- From 2000-2005, marketing expenses for Altace in the U.S. were as follows:
  - 2000: approximately \$1.5 million.
  - 2001: approximately \$80.4 million.
  - 2002: approximately \$92.7 million.
  - 2003: approximately \$75.3 million.

- 2004: approximately \$55.1 million.
- 2005: approximately \$51.8 million.

In their stipulation, the parties agreed that “net sales = gross sales - customary trade allowance, rebates, discounts and returns.” Stipulation of Facts at 2 n.1.

In addition, the Court makes the following findings:

- Between 1991-1999, Altace’s market share by total of prescriptions for ACE-inhibitors never exceeded approximately 5.5 percent. Maness at 1679: 14-17.
- Between 1991-1999, the market leaders were Enalapril and Lisinopril based on the number of prescriptions. Maness at 1680: 13-17.
- There is no evidence that doctors proscribe Altace based on its isomeric purity. Wharton at 715.
- At its height, Altace’s market share based on number of prescriptions was twelve percent. Maness at 1642: 21-24. From 1999 to 2005, Altace’s market share rose from four percent to twelve after the HOPE Study was released and its indication was approved by the FDA. Maness at 1714: 8-14; 1721: 18-23. This increase was the result of an intense marketing campaign based on the outcomes of the HOPE study.
- Altace was never marketed on the ground that it is “substantially free of other isomers.”
- Wyeth’s co-promotion agreement with King resulted in King paying Wyeth approximately \$220 million in 2005. Maness at 1696-97; McSorley at 1951: 18-21. Since 2001, as of December 2005, the total promotional fee King has paid Wyeth or is due Wyeth is more than \$800 million. McSorley at 1951: 22-25. This is one-third of King’s sales since entering into the agreement in 2000. McSorley at 1952: 17-24.
- Since the HOPE Study was released, Schering made more than \$48 million by licensing the ‘258 patent for a 2.5% royalty based on Altace’s net sales. Wyeth made more than \$800 million by co-promoting the product. McSorley: 1948: 22-1949: 15; 1951: 22-1952: 7.

### **III. Conclusions of Law: Validity of the ‘722 Patent**

Because a patent is presumed valid, 35 U.S.C. § 282,<sup>16</sup> the standard of proof for invalidity is higher than the standard of proof for infringement. Unlike the standard of proof for infringement, which is preponderance of the evidence, the party challenging a patent bears the burden of showing invalidity by clear and convincing evidence. Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1339 (Fed. Cir. 2003). Here, Lupin has attacked the validity of the '722 patent by arguing anticipation, obviousness, and lack of enablement. The Court will address these arguments in turn.

#### **A. Anticipation**

A product or process must be new in order to be patentable. Thus, under 35 U.S.C. § 102, anticipation “requires that there be an identity of invention.” Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 619 (Fed. Cir. 1985). A patent is invalid for anticipation – lack of novelty – “if a single prior art reference discloses each and every limitation of the claimed invention.” Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003). “A prior art reference may anticipate,” however, “without disclosing a feature of the claimed invention if that missing feature is necessarily present, or inherent, in the single anticipating reference.” SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005) (quoting Schering Corp., 339 F.3d at 1377 with approval); see also Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006) (“Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently.”).

Determining whether something is new requires comparing the claimed product with the

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<sup>16</sup>35 U.S.C.A. § 282 provides in relevant part:

A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim . . . .

products of the relevant prior art. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d. 1313, 1335 (Fed. Cir. 2002). “Prior art,” however, “can be an elusive concept because it is not defined in the patent statute, nor is there an all inclusive definition in the case law or literature.” HERBERT SCHWARTZ, PATENT LAW AND PRACTICE § 4.I.C (4th ed. 2003). Nevertheless, sections 102(a),(e) and (g) of Title 35 address prior art with respect to novelty, id., and

[s]ections 102(a) and (b) operate in tandem to exclude from consideration for patent protection knowledge that is already available to the public. They express a congressional determination that the creation of a monopoly in such information would not only serve no socially useful purpose, but would in fact injure the public by removing existing knowledge from public use.

Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 148 (1989). The relevant sections of 35 U.S.C. § 102 when determining prior art provide:

A person shall be entitled to a patent unless--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

...

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language; or

...

(g)(1) during the course of an interference conducted under section

135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Moreover, anticipation requires a prior art disclosure to be “enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation.” Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005). While this seems like a straightforward standard in the patent context, it is not, as “[t]he standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112.” Id. (citation omitted).

While section 112 provides that the specification must enable one skilled in the art to “use” the invention, section 102 makes no such requirement as to an anticipatory disclosure. Significantly, we have stated that anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.

Id. (internal quotations and citations omitted). Accordingly, when determining anticipation, it is not “necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.” Id. (citing with approval In re Donohue, 766 F.2d 531, 533 (Fed. Cir.1985)).

# **1. The ‘258 Patent**

Lupin maintains that the ‘258 Patent qualifies as prior art under 35 U.S.C. § 102(a) and (b) and is enabled. According to Lupin, based on the disclosure of the ‘258 patent, its claims, and its relationship to the ‘886 application, one skilled in the art would have been able to prepare, identify,

purify and use the 5(S) isomer of Ramipril. Moreover, even if the ‘258 patent provided for only a mixture of Ramipril isomers, a person of ordinary skill in the art could envisage each member of this limited class of compounds, which would include Ramipril in the 5(S) configuration substantially free of other isomers as found in claim 1 of the ‘722 patent. Therefore, in Lupin’s view, the ‘258 patent disclosed a small genus that anticipated the species of that genus, namely ramipril in the 5(S) configuration substantially free of other isomers.

Aventis, of course, disagrees, arguing that a disclosure of a mixture of isomers does not constitute a disclosure of a specific isomer. In Aventis’ view, Lupin has not shown that a prior art reference discloses Ramipril substantially free of other isomers and that a mixture containing Ramipril along with several other isomeric versions of Ramipril is insufficient to anticipate. In addition, Aventis maintains that Example 20, the prior art reference Lupin relies on based on the ‘258 patent’s relationship to the ‘886 application, is not enabled and thus cannot be anticipated.<sup>17</sup> Aventis also argues that Ramipril is one of millions of compounds that falls within the genus of claim 1 of the ‘258 patent. A genus, according to Aventis, does not anticipate a species.

Aventis also maintains that the ‘258 patent is not prior art because the PTO issued the ‘258 patent based on the ‘390 application in which “new matter” that included an example for making Ramipril was added. In addition, according to Aventis, although the “old” matter in the ‘258 patent originally had a claim to Ramipril (see claim 3), Schering disclaimed this claim, “[telling] the world that it did not invent [R]amipril.” Pl.’s Tr. Mem. at 6.

In discussing the ‘258 patent, the Court begins with the enablement prong as it is the easiest, given that the Court has **FOUND** that Aventis conceded that the ‘258 patent was enabled when it

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<sup>17</sup>As noted supra, the Court refers to Example 20 in this context with the understanding that the ‘258 patent actually includes the Example in parts and under a different numbering scheme. See supra II.D.16.

licensed it from Schering, requested an extension of the patent before the PTO, and relied on it to receive FDA approval for Altace. See supra at II.D.16. The Court has great difficulty finding that the ‘258 patent was not enabled for the purposes of anticipation under these circumstances. To conclude otherwise, the Court would essentially be finding that Aventis misrepresented the ‘258 patent’s validity before the PTO and the FDA.

Whether the ‘258 patent constitutes “prior art” for the purposes of anticipation is a much closer question. Fortunately for the Court, however, two arguments made by Aventis are quickly dispensed with. First, regarding Aventis’ disclaimer argument, the Court observes that Aventis provides no legal support for its contention that a disclaimer means that the disclaimant has “told the world that it did not invent” something and thus cannot be considered prior art. Pl’s Pre-Trial Br. at 6. The Disclaimer statute is as follows:

Whenever, without any deceptive intention, a claim of a patent is invalid the remaining claims shall not thereby be rendered invalid. A patentee, whether of the whole or any sectional interest therein, may, on payment of the fee required by law, make disclaimer of any complete claim, stating therein the extent of his interest in such patent. Such disclaimer shall be in writing, and recorded in the Patent and Trademark Office; and it shall thereafter be considered as part of the original patent to the extent of the interest possessed by the disclaimant and by those claiming under him.

35 U.S.C. § 253 (emphasis added). MOY’S WALKER ON PATENTS explains:

Section 253 of the patent statute authorizes the patentee to file two types of disclaimers. The first applies to individual claims in the patent, and involves the patentee relinquishing all rights under the claim. The second relinquishes a terminal part of the time span of the patent right in the patent as a whole.

MOY’S WALKER ON PATENTS § 3:67 (4th ed. 2005) (emphasis added). As the Court found supra, Schering relinquished claims 3-6 of the ‘258 patent and licensed the patent to Aventis for a 2.5% royalty to last the life of the patent. The evidence undoubtedly shows that Schering licensed the ‘258

patent to Aventis precisely because Schering did invent something, namely, a compound that included the Ramipril molecule. See supra II.D.29. Moreover, in exchange for the royalty, Schering relinquished all rights to claims 3-6 of the ‘258 patent. Indeed, in order to request an extension of the ‘258 patent, Aventis included in its letter to the PTO that it could act on Schering’s behalf precisely because Schering made Aventis its agent with respect to the ‘258 patent and also had filed a disclaimer. Id. In short, relinquishing rights to a claimed invention – or as the statute puts it, “stating therein the extent of his interest in such patent” – is far different from declaring that one never invented it. The Court is not persuaded by the bald and unsupported assertions Aventis makes otherwise.

With respect to Aventis’ “old” versus “new matter” argument, the Court also disagrees. As described in the chronology supra, the ‘258 patent, on its face, claims priority to the ‘484 and ‘886 applications. Based on the ‘886 application, the Court found that the ‘258 patent had an effective filing date of October 23, 1980. See supra II.D.3. The Court also found that the first disclosure of Ramipril as part of a mixture that included the 5(S) configuration occurred on October 23, 1980, which is the filing date of the ‘886 application. The fact that the ‘390 application, which was filed on July 30, 1984, disclosed “new” material simply does not change the fact that a mixture of Ramipril with the 5(S) configuration was disclosed as part of Example 20 in the October 23, 1980 application. The “new” versus “old” matter argument is a distraction and the Court **FINDS** that the ‘258 patent is prior art.<sup>18</sup>

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<sup>18</sup>The Court observes that Lupin could question Aventis’ November 5, 1981 priority date for the same reasons, as whether that date would encompass “substantially free of other isomers” is suspect, given that the German patent application giving the ‘722 patent this priority date does not include this phrase or even Ramipril in the 5(S) configuration in isolation. The PTO itself made a point to note that Aventis did not claim the “*cis* compound exclusively” until December 18, 1984. See supra at II.D.13.

The real questions are the following: 1) whether the single prior art reference that is Example 20 disclosed each and every limitation of the claimed invention in the ‘722 patent; and 2) whether the ‘258 patent inherently anticipated the 5(S) configuration of Ramipril substantially free of other isomers based on a genus/species relationship between the ‘258 and ‘722 patents.

The Court **FINDS** that the ‘258 patent does not disclose each and every limitation of the ‘722 patent. The Court has found that the ‘258 patent, like the ‘944 patent, includes an enabled example which resulted in a “mixture” of two isomers – the 5(S) and the S,S,S,S,R – of Ramipril. See supra II.D.4, II.D.5, and II.D.16. The Court does not find, however, that this prior art reference disclosed Ramipril in the 5(S) configuration “substantially free of other isomers.” Consequently, it cannot find that this single prior art reference disclosed each and every limitation of the claimed invention in the ‘722 patent, namely Ramipril in the 5(S) configuration “substantially free of other isomers.” Schering Corp., 339 F.3d at 1377. The limitation “substantially free of other isomers” simply is not there. Nor was the mixture shown to be one in which the 5(S) configuration was substantially free of the S,S,S,S,R isomer or any other isomer. Therefore, at least in this respect, the Court cannot find anticipation.

The harder question is whether the ‘258 patent may be considered to be a prior art reference that discloses a “genus” and thus, if sufficiently small, serves to inherently anticipate a later-named “species.” Of course, the fact that a prior art reference discloses a genus does not necessitate the conclusion that all resulting species were inherently disclosed. Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (“A prior art reference that discloses a genus still does not inherently disclose all species within that broad category.”); Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) (“Under [defendant’s] theory, a claim to a genus would inherently disclose all species. We find [this] argument wholly meritless

. . . .”); In re Meyer, 599 F.2d 1026 (C.C.P.A. 1979) (declining to find that a disclosed genus anticipated a species because the “genus, ‘alkaline chlorine or bromine solution,’ does not identically disclose or describe . . . the species alkali metal hypochlorite, since the genus would include an untold number of species.”). Rather, the disclosure of a “small genus may anticipate the species of that genus.” Bristol-Myers Squibb Co. v. Ben Venue Lab., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001) (emphasis added). This is so “even if the species are not themselves recited.” Id.; see also Atofina, 441 F.3d at 999 (explaining that “a very small genus can be a disclosure of each species within the genus.”). Accordingly, the rule is a narrow one, as finding that a genus anticipates a species requires a court to examine the number of compounds embraced by the genus, the closeness of their relation, and whether the species can be “at once envisaged” from the formula by a person of ordinary skill in the art without having to speculate, combine disclosures not related to each other, or choose indiscriminately from possible combinations. See In re Petering, 301 F.2d 676, 681 (C.C.P.A. 1962) (holding in a case involving twenty compounds that a general chemical formula will anticipate a claimed species covered by the formula when the species can be ‘at once envisaged’ from the formula); In re Ruschig, 343 F.2d 965, 974 (C.C.P.A. 1965) (narrowing, in a case involving 130 to 156 very different compounds, Petering’s focus by disapproving of “mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them” and “hindsight anticipations”); In re Schaumann, 572 F.2d 312, 316 (C.C.P.A. 1978) (relying on Petering to conclude that claims to a specific compound were anticipated because they “embrace[d] a very limited number of compounds closely related to another” and that the “blood pressure lowering effect of [the compound was] also shared by the class of compounds disclosed by [the genus patent].”); In re Parameswar Sivaramakrishnan, 673 F.2d 1383, 1384-85 (C.C.P.A. 1982) (applying Petering and finding anticipation because one of ordinary

skill in the art would not have to “speculate” or “choose judiciously from a genus of possible combinations” to arrive at the claimed invention where a genus disclosed approximately 70 salts); Metabolite Labs., 370 F.3d at 1367 (upholding a finding of no anticipation where the prior art reference disclosed “no more than a broad genus of potential applications of its discoveries” and that the genus simply invited investigation to discover other uses).<sup>19</sup>

To support its genus/species argument, Lupin relies heavily on In re Thomas, 178 F.2d 412, 415-16 (C.C.P.A. 1949), a case, notably, that has been cited only once since. Thomas involved a composition of insecticides, and the party seeking the patent argued that the patent claims which related to the “gamma isomer of the compound” were separately patentable from the prior art “mixture of isomers containing a substantial portion thereof.” Id. at 413. The Patent Examiner rejected the patent, and the Board of Appeals for the United States Patent Office affirmed. The Court of Customs and Patent Appeals also affirmed the rejection, observing that the “gamma isomer of benzene hexachloride is an old composition” and thus “the state of the prior art was apply sufficient to suggest the use of the gamma isomer as an insecticidal composition.” Id. at 415. The

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<sup>19</sup>To support its inherency argument, Lupin also relies on Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999), which stated:

. . . when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim. In chemical compounds, a single prior art species within the patent’s claimed genus reads on the generic claim and anticipates.

Id. at 1346 (internal citations omitted). The problem with Lupin’s reliance on this case is that it involved a species that was patented prior to the genus. The case before the Court here, in contrast, involves a genus patented before an alleged species. As a review of MOY’S WALKER ON PATENTS reveals, whether the genus or the species is patented first changes the analysis. See § 8:13 (noting that, “[s]omewhat more complicated are situations in which the invention at issue is a specie, and the potentially anticipating reference is couched in terms of the genus” and describing a different line of cases addressing the issue).

appellate court also noted that the insecticidal activity “was due almost entirely to the presence of the gamma isomer.” Id. at 414. The appellate court thus affirmed the PTO Examiner’s rejection of the patent “as failing to distinguish adequately from the old composition comprising the crude mixture of all four isomers which are disclosed in the [prior art] patent as a satisfactory insecticide.” Id. at 415.

The Court finds Thomas distinguishable for several reasons. First, because it was an appeal of the PTO Examiner’s rejection of a patent, the clear and convincing standard that is Lupin’s burden here did not apply. Second, unlike the gamma isomer, which was found to be an “old composition,” the specific isomer at issue in this case is Ramipril in the 5(S) configuration in essential isolation, which is not an “old composition” found in the prior art. Third, Thomas involved an insecticide – the toxicity of the compound is precisely its value. The situation before the Court is much different. Although the toxicity of other Ramipril isomers has not been proven one way or the other, it is arguably the absence of toxicity that contributes to Altace’s effect. See Mosberg 1311: 15-25 (explaining how small changes cause toxic results).<sup>20</sup> This is probably why more recent decisions dealing with drug compounds reveal that courts are far less inclined to assume that a mixture of isomers makes no difference. See Pfizer Inc. v. Ranbaxy Labs Ltd., 405 F. Supp. 2d 495, 519 (D. Del. 2005) (finding, in a pharmaceutical case involving the drug Lipitor, that although the genus patent mentioned “calcium as one of the seven listed pharmaceutically acceptable salts,” it did not mention the R isomer of “atorvastatin calcium,” the species compound claimed in the subsequent patent and thus no anticipation or obviousness); Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp.2d 713 (N.D. W.Va. 2004) (finding, in a pharmaceutical case involving the compound

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<sup>20</sup>A famous example of a drug having undesirable side effects based on its stereochemistry is Thalidomide. The S-enantiomer of the Thalidomide compound prevented morning sickness. The R-enantiomer of the compound, on the other hand, caused severe birth defects. Mosberg at 31: 8-11.

levofloxacin, that a claim to the S isomer of a compound was patentable over a disclosure in the prior art of a mixture having both the R and S isomer of that compound), aff'd 05-1222 (Fed. Cir. Dec. 19, 2005); In re May, 574 F.2d 1082 (C.C.P.A. 1978) (finding, in a pharmaceutical case involving a pain-relieving drug, that stereoisomers are prima facie obvious but that the prima facie case was rebutted because it was shown that the isomers at issue had different properties and the properties of the drug could not be reliably predicted on the basis of chemical structure). But see In re Adamson, 275 F.2d 952 (C.C.P.A. 1960) (affirming, in a pharmaceutical case, the PTO's rejection of a claim for obviousness because a person of ordinary skill in the art would have recognized that the compounds at issue were racemates that could be separated).

In any event, in applying the genus/species analysis, the Court first **FINDS** that, as the '258 genus embraced two compounds, the S,S,S,S,S version of Ramipril and the S,S,S,S,R version, the number of species included in the '258 patent genus is small. When the example related to Ramipril is followed, the genus does not embrace "billions" or "millions" of possible compounds as Aventis/King so strenuously urged but only two. The Court also **FINDS** that these two compounds are closely related, as they are stereoisomers of the same molecule and have almost identical configurations. The difficult question is whether the species – specifically the 5(S) configuration in isolation – can be "at once envisaged" from the '258 patent by a person of ordinary skill in the art without having to speculate, combine disclosures not related to each other, or choose indiscriminately from possible combinations.

In this case, the Court has found that the '258 patent specifically encompasses the molecular structure of Ramipril in the 5(S) configuration. What it does not encompass, however, is Ramipril "substantially free of other isomers." While the Court has no doubt that a person of ordinary skill in the art would have been able to envisage Ramipril in the 5(S) configuration, the Court does have

some doubt that a person of ordinary skill in the art would have “envisaged” a substantially pure version of Ramipril in the 5(S) configuration by itself as preferable to a mixture of two Ramipril isomers. Although the Court is not satisfied that Aventis has adequately communicated what “substantially free of other isomers” actually does for Ramipril, Lupin has not shown the Court that the phrase is meaningless either. In fact, Lupin’s argument that the other isomers of Ramipril are inert and thus of no effect mitigate against its contention that someone of ordinary skill in the art would have envisaged Ramipril in the 5(S) configuration substantially free of other isomers. If the other isomers are thought to be inert, why would someone of ordinary skill envision them separately?

Undoubtedly, the Court is disturbed by the fact that Aventis represented to the PTO when it asked for an extension of the ‘258 patent that the “sole active ingredient” was found in the formula of Ramipril in the ‘258 patent. Pl.’s Ex. 384 at 597; see supra II.D.29. This suggests that having an isomeric mixture of Ramipril makes no therapeutic difference. On the other hand, the evidence shows that some Ramipril isomers other than the 5(S) configuration have therapeutic potency. See infra II.D.23. The Court thus cannot assume that a mixture of Ramipril with different therapeutic potencies would make no difference as long as the 5(S) configuration predominated the mixture. See Ortho-McNeil, 348 F. Supp. 2d at 729, 763-64 (concluding that a claim to an all-S isomer is patentable over a disclosure containing a mixture of isomers); May, 574 F.2d at 1090 (holding that a claim to just the R or S isomer was not anticipated by a prior art mixture); In re Schechter, 205 F.2d 185, 191 (C.C.P.A. 1953) (unpredictability considered as a factor weighing against a conclusion of obviousness of the claimed compounds). Moreover, Lupin has the heavy burden on this point. Given that everyone seems to agree, including Lupin’s experts, that the 5(S) isomer is preferred, the Court is not clearly convinced that a mixture of isomers containing the 5(S) isomer is necessarily equal to a substantially pure compound with the 5(S) isomer. Certainly, the Court is not clearly

convinced that one of ordinary skill in the art would have envisaged such, even if such a person knew that the 5(S) configuration of Ramipril had the most potent therapeutic utility out of all of the other possible isomers. The bottom line is that the ‘722 patent essentially claims Ramipril in the 5(S) configuration in isolation. Although there is some suggestion that Dr. Smith recognized this possibility and perhaps even isolated the 5(S) isomer, there is not enough clear and convincing evidence to persuade this Court to find that the ‘722 patent, which is a species, was anticipated by the ‘258 patent genus. See Pfizer, 405 F. Supp. 2d at 514-15 (in an obviousness analysis, concluding that, although the species patent specifically claimed the active ingredient in the genus patent, there was no infringement).

## 2. The ‘944 Patent and the Schering References

Lupin maintains the ‘944 patent qualifies as prior art under 35 U.S.C. § 102(e) because a person of ordinary skill in the art could readily envision, by means of Example 20 disclosed in the ‘944 patent’s prior art, the compound consisting of the 5(S) configuration of Ramipril. Aventis argues that the ‘944 Patent is not prior art because Example 20 in the ‘944 Patent does not work.

The Court **FINDS** that the ‘944 patent, like the ‘258 patent, contains an enabled example which resulted in a “mixture” of two isomers – the 5(S) and the S,S,S,S,R – of Ramipril. As noted supra, the Court did not find, however, that this prior art reference disclosed Ramipril in the 5(S) configuration “substantially free of other isomers.” Consequently, the analysis applied with respect to anticipation and the ‘258 patent is the same. The Court cannot find that this single prior art reference disclosed each and every limitation of the claimed invention in the ‘722 patent, namely Ramipril in the 5(S) configuration “substantially free of other isomers.” Nor can it find that the Schering scientists envisioned Ramipril in the 5(S) configuration “substantially free of other isomers.” Accordingly, the Court **FINDS** that the 5(S) configuration of Ramipril substantially free

of other isomers in the '722 patent was not anticipated by the '944 patent and the Schering References leading up to it.

### **3. Sample SCH 31925**

Lupin maintains that Dr. Smith's physical preparation of sample SCH 31925 qualifies as prior art under 35 U.S.C. § 102(g), maintaining that "United States does not permit the first person to file a patent application to receive patent rights if someone else in the United States invented the subject matter first." Lupin also argues that, because Aventis/King has not limited its claims to only the pure 5(S) isomer, Dr. Smith was not obligated to make her 5(S) isomer pure to show prior invention. Moreover, according to Lupin, the proper analysis turns on whether Dr. Smith actually conceived the invention's structure and an operative method of making it.

Aventis/King contends that SCH 31925 fails to anticipate because, as it is a mixture, it does not meet every element of the claimed invention, emphasizing that Dr. Smith never separated the mixture into its individual component isomers. Aventis/King also argues that SCH 31925 is not a prior art reference because Lupin failed to show that Dr. Smith had a contemporaneous appreciation of what isomers were in the SCH 31925 sample. Finally, Aventis/King maintains that SCH 31925 is not prior art because non-public laboratory work does not qualify as prior art if it is "abandoned, suppressed, or concealed."

"Section 102(g) operates to ensure that a patent is awarded only to the 'first' inventor in law." Apotex U.S.A. Inc. v. Merck & Co., Inc., 254 F.3d 1031, 1035 (Fed. Cir. 2001). In addition to determining priority in interference proceedings, § 102(g) may also be asserted as a defense to an infringement suit. Id. In such an instance, the party asserting the defense must present, by clear and convincing evidence, that the invention was made by another, prior, inventor. Id. at 1037-38. Thus a "patent may be invalid as anticipated due to the prior conception and reduction to practice by

another of the patentee's invention.” Texas Instruments Inc. v. U.S. Intern. Trade Com’n, 988 F.2d 1165, 1177 (Fed. Cir. 1993).

In this case, there is no question that Dr. Smith prepared a substance in SCH 31925 that contained the 5(S) configuration of Ramipril and that this sample was based on Example 20 provided in the ‘886 application. See supra at II.D.3 and 4. The problem is that SCH 31925 was a mixture and not Ramipril in the 5(S) configuration substantially free of isomers. Accordingly, as with the ‘258 patent and the ‘944 patent, the Court cannot find by clear and convincing evidence that SCH 31925 is a prior art reference disclosing Ramipril in the 5(S) configuration substantially free of other isomers. The Court also cannot find by clear and convincing evidence that Dr. Smith conceived of the 5(S) isomer separate and apart from the S,S,S,S,R isomer that was part of the SCH 31925 mixture. As noted supra, she certainly envisioned the 5(S) isomer, just as she “contemplate[d] all possible isomers.” See II.D.2 (quoting Smith at 766: 16-767: 2. What Lupin has not shown by clear and convincing evidence, however, is that she envisioned the 5(S) configuration of Ramipril “substantially free of other isomers” in its essential isolation. She also never committed to narrowing down the compound to one isomer. Although she did comment that “it was hoped that it would be narrowed down,” this narrowing could have included two or three isomers. Id. Thus the Court cannot **FIND** by clear and convincing evidence that Dr. Smith conceived of Ramipril in the 5(S) configuration substantially free of other isomers. Clear and convincing evidence is much stronger than preponderance of the evidence. One may apply while the other may not.

## **B. Obviousness**

An invention must be nonobvious to a person of ordinary skill in the art in order to receive patent protection. In re Kahn, 441 F.3d 977, 985 (Fed. Cir. 2006). Under 35 U.S.C. § 103(a),

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the

differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

When determining whether an invention would have been obvious, the legal question is this: are the differences between the subject matter sought to be patented and the prior art such that the subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art? Kahn, 441 F.3d at 985. “Obviousness may not be established using hindsight.” Kahn v. Gen. Motors Corp., 135 F.3d 1472, 1479 (Fed. Cir 1998), cert. denied, 525 U.S. 875 (1998). In addition, when determining obviousness, “the invention must be considered as a whole and the claims must be considered in their entirety.” Id. at 1479-80.

As established by Graham v. John Deere Co., 383 U.S. 1, 17 (1966), in order to reach the legal question of obviousness, a court is required to make the following factual determinations: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims at issue; and, 3) the level of ordinary skill in the pertinent art. See also Ruiz v. A.B. Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000) (stating “[o]ur precedent clearly establishes that the district court must make Graham findings before invalidating a patent for obviousness.”). In addition, in order to avoid applying hindsight, a court must weigh “secondary considerations of nonobviousness.” Id. at 662, 667. Secondary considerations of nonobviousness “include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results.” Id. at 662-63.

With respect to chemical compounds, however, a prima facie case of obviousness is established when there is “structural similarity between claimed and prior art subject matter [and] where the prior art gives reason or motivation to make the claimed compositions.” Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting Dillon,

919 F.2d 688, 692 (Fed. Cir. 1990)). “[A] reasonable expectation of success, not absolute predictability” supports a conclusion of obviousness.” Id. Thus, Lupin must prove: 1) that the prior art would motivate a person of ordinary skill in the art to make Ramipril in the 5(S) configuration substantially free of other isomers, and 2) that the prior art “reasonably suggest[s] that the compound would exhibit its unique combination of properties.” Ortho-McNeil, 348 F. Supp.2d at 749.

While this is the general standard for chemical compounds, Lupin maintains that the Court of Appeals for the Federal Circuit has held that stereoisomers are prima facie obvious and therefore the analysis apparently ends. In Dillon, the appellate court indeed stated:

[I]f an examiner considers that he has found prior art close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a prima facie case of obviousness. The burden then shifts to the applicant, who then can present arguments and/or data to show that what appears to be obvious, is not in fact that, when the invention is looked at as a whole.

919 F.2d at 696 (internal citations omitted). Moreover, in Jones, the Court of Appeals for the Federal Circuit enumerated the categories of structural chemical similarity that have given rise to prima facie obviousness, and one of these categories is stereoisomers. In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (listing In re May, 574 F.2d 1082 (C.C.P.A. 1978) as standing for this proposition). However, in its more recent decision in In re Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997), the Federal Circuit applied the Graham factors to an isomeric compound. Ortho-McNeil, 348 F. Supp.2d at 749 n.19. Therefore, while it appears that stereoisomers may be prima facie obvious, there is no per se rule. Thus, even when stereoisomers are involved, a court must be careful “[t]o prevent the distortions of hindsight” and pay “close attention to the supposed reason or motivation for making the claimed compound is critical.” Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2001

WL 1397304, \*5 (S.D. Ind. 2001). As CHISUM ON PATENTS explains,

Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Further, many such new compounds are obvious in the sense that any competent chemist could have synthesized them if requested or motivated to do so.

2 DONALD S. CHISUM, CHISUM ON PATENTS § 5.04 (2000) [hereinafter “CHISUM ON PATENTS”] (cited in Eli Lilly, 2001 WL 1397304, \*5) . Accordingly, even with chemical compounds, when finding motivation or suggestion, “there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings [and thus these findings] should be made with a complete understanding of the first three ‘Graham factors.’” Id.<sup>21</sup>

### **1. The Scope and Content of the Prior Art**

As the findings of fact indicate, the prior art includes the Schering references, the ‘258 patent, Dr. Smith’s work and the teachings involving Captopril, Enalapril, snake venom from the Brazilian viper, and other ACE-inhibitors.

### **2. One of Ordinary Skill in the Art**

Obviousness turns on “the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains.” In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). In this way, a court must distinguish between the actual inventor’s skill and the skill of a person of ordinary skill in the art. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985).

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<sup>21</sup>If prima facie obviousness is found, the patent owner may rebut the finding by offering evidence of unexpected results. Dillon, 919 F.2d at 692-93. “Rebuttal may take the form of ‘a comparison of test data showing that the claimed compositions possess unexpectedly improved properties . . . that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument . . . that is pertinent.” Mayne, 104 F.3d at 1342 (quoting Dillon, 919 F.2d at 692-93). Because the Court does not find that separating the stereoisomers in this case was prima facie obvious, rebuttal on this point was not necessary.

The actual inventor's skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something-call it what you will-which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done, faced with the revelations of references.

Id. Accordingly, "[a] person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights . . . ." Id.

As found supra, a person of ordinary skill in the art in this case would be someone with a Ph.D. in chemistry or organic chemistry with knowledge of stereochemistry, or have a similar amount of training in association with preparing chemical compounds in the pharmaceutical industry. Such a person would be familiar with stereochemistry and with methods for preparing, isolating, and characterizing pharmaceutical compounds. For the purposes of this obviousness analysis, such a person is not an innovator who conducts expensive, systemic research or is given to extraordinary insights.

### **3. \_\_\_\_\_ Differences between the Prior Art and the Claims at Issue—Prima Facie Obviousness**

Lupin argues that Ramipril in the 5(S) configuration substantially free of other isomers is prima facie obvious in view of the Schering references as well as prior art disclosures related to Merck's Enalapril. Aventis/King maintains that Example 20, if it worked, discloses a mixture of compounds and that nothing in the prior art would have motivated someone to select a compound having all of its chiral carbons in the S-configuration.

The Court has little problem finding that the structural similarity between the diastereomeric mixture Dr. Smith created – the S,S,S,S isomer and the S,S,S,S,R isomer – and Ramipril in the

5(S) configuration substantially free of other isomers are similar. Not only are the chemical building blocks the same, but the chiral carbons are almost identical. The questions are whether the prior art “gives reason or motivation to make the claimed compositions,” namely Ramipril in the 5(S) configuration substantially free of other isomers, and whether the prior art would reasonably suggest that the compound would exhibit its unique combination of properties.

Lupin fails to persuade this Court by clear and convincing evidence on the first question, whether the prior art would motivate someone of ordinary skill in the art to make Ramipril in the 5(S) configuration substantially free of other isomers. Lupin argues that the Schering references teach an overwhelming preference for (S) and single isomers. Specifically, Lupin maintains that the ‘944 patent taught a preference for the all-(S) isomer by itself, as it includes a statement that the isomers of the Examples should be isolated. Def.’s Ex. 301, col. 15, lines 10-15; col. 10, lines 28-41. Moreover, according to Lupin, additional teachings outside of the Schering references would direct a person of skill in the art to a single all-(S) isomer, not one that is part of a mixture. These teachings include: the fact that the snake venom of the Brazilian viper, Captopril, and Enalapril are all-(S) single isomer compounds; that Merck’s publication of Enalapril’s structure in Nature taught that, if the all-(S) configuration in Enalapril was not followed, “significant potency was lost . . . about a 700-fold difference,” see id. at II.D.1; that Merck stated in their published papers that the stereochemistry had important design implications for the synthesis of other inhibitors; that Merck reported it obtained high, if not entire, purity for its all-(S) isomer; and that ACE-inhibitors are amino acid derivatives, all of which, except for one (cystine) have the S-configuration.

In response, Aventis/King maintains that the (S) configuration in the chiral centers in snake venom, Captopril, and Enalapril occur in the “side chain” portion of the Ramipril molecule. The Ramipril molecule is distinct from these compounds in that it includes the 5,5 bicyclic ring, which

created the “bridgehead” portion of the Ramipril molecule not present in the snake venom, Captopril or Enalapril. As for the ‘944 patent teaching a preference for the all-(S) isomer by itself, Aventis/King points out that Lupin is relying on a part of the ‘944 patent description of a 6,5 compound instead of the 5,5 compound at issue in this case. Finally, Aventis/King argues that only hindsight allows Lupin to assert that Ramipril’s other isomers are inactive. When the ‘722 patent was issued, according to Aventis/King, “it was not known that the other isomers were inactive” and thus “one skill in the art would not have known that the other isomers conferred no medical benefit.” Pl.’s Post-Trial Br. at 24-25.

Although it is very a close question, given that the standard is clear and convincing evidence, the Court **FINDS** that a person of ordinary skill in the art would not by clear and convincing evidence have necessarily been motivated to isolate Ramipril in the 5(S) configuration substantially free of other isomers. First, the Court is not persuaded by clear and convincing evidence that the snake venom, Captopril, and Enalapril would have motivated a person of ordinary skill in the art to combine the teachings in the Schering references and/or the ‘944 patent to arrive at (S) isomers in the bridgehead portion of the Ramipril molecule. The experts in this case agree that the snake venom, Captopril, Enalapril, and the Nature article discussing Enalapril do not describe the bicyclic configuration found in the bridgehead portion. Ganem at 367: 18-25; 368: 1-25; Mosberg at 1319: 9-12; 1321: 24-25; 1322: 1-15; 1490: 11-14. Moreover, Dr. Smith testified that neither Captopril nor Enalapril provided any information on the bridgehead atom’s stereochemistry. Smith at 953: 5-15. While in hindsight it seems obvious that Ramipril would likewise be in the all-S configuration, the Court must be wary of that temptation given that bridgehead portion of the Ramipril molecule does not replicate any structure in the snake venom, Captopril, or Enalapril. The Court observes that another ACE-inhibitor, Trandolapril, which, unlike Captopril or Enalapril, has a bridgehead, has an

S and an R in the two chiral centers of the bridgehead. Mosberg at 1325: 3-7. Finally, even if it was obvious that the preferred isomer of Ramipril would be in 5(S), that does not necessitate the conclusion that the 5(S) version should be as free from other isomers as possible. The Court **FINDS** that the prior art does not by clear and convincing evidence show that a person of ordinary skill in the art would be motivated to make Ramipril in the 5(S) configuration substantially free of other isomers. It is the isolation of the 5(S) isomer from a mixture of Ramipril isomers that gives the Court the most concern, especially in light of the difference between the preponderance of the evidence and the clear and convincing evidence standards.

The Court is also not persuaded by clear and convincing evidence that the '944 patent taught a preference for the 5(S) isomer by itself either. The '944 patent states: "When diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods." Def.'s Ex. 301, col. 15, lines 10-15; col. 10, lines 28-41. What this indicates to the Court is that, if a diastereomer is made, it may be separated. There is no suggestion, however, that it should be separated or that its separation necessarily results in the all-S isomer. Finally, as Aventis/King points out, this portion of the patent is referring to a 6,5 compound having a "cis, syn" configuration and not a 5,5 compound, which is Ramipril. If the standard was preponderance of the evidence, the Court might determine that a person of ordinary skill in the art would apply the same configuration from one ring-structure to another. That is not the standard, however, and, even if the Court found as much, the problem of isolating the 5(S) configuration remains. In other words, regardless of what the 6,5 ring system taught to a person of ordinary skill in the art, the '944 patent does not clearly motivate that person to create a substantially pure isomeric version of Ramipril.

The Court also agrees with Aventis/King that the evidence shows that, as of 1981, there was

no expectation that Ramipril substantially free of other isomers would be more or less potent than a mixture. While it is clear that the 5(S) configuration is preferred, it simply is not clear that this preference related to the 5(S) configuration being separate from other isomers. As the Finding of Facts indicate, nor was this separation particularly easy to do. Put another way, having other isomers in the mixture did not seem to be of great concern to the Schering scientists – indeed, it did not seem to be of great concern to the Aventis scientists until they could not get their own patent approved. Accordingly, the Court is not persuaded by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to isolate Ramipril in the 5(S) configuration substantially free of other isomers.<sup>22</sup>

With respect to secondary considerations, which must be weighed even though the Court is not persuaded by clear and convincing evidence on the motivation element, the Court is not convinced that the evidence establishes that the invention of Ramipril in the 5(S) configuration was not obvious. First, with respect to Aventis/King’s argument that Altace is a commercial success, the Court **FINDS** that there is no evidence linking the fact that Ramipril is “substantially free of other isomers” to Altace’s success. A “nexus must be established between the merits of the claimed invention and evidence of commercial success before that evidence may become relevant to the issue of obviousness.” Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1324 (Fed. Cir. 2004) (citation omitted). Aventis/King has shown no nexus whatsoever between Altace’s success and the drug being “substantially free of other isomers.” Instead, Aventis/King’s argument seems to be that, because “substantially free of other isomers” is in the ‘722 patent, any commercial success

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<sup>22</sup>Because the Court finds there was no motivation for a person of ordinary skill in the art to separate the mixture, it is not necessary for the Court address whether the prior art would “reasonably suggest” that “the compound would exhibit its unique combination of properties.” See Ortho-McNeil, 348 F. Supp.2d at 749.

that Altace had is per se related to this attribute. This is hard for the Court to accept, however, when Aventis/King admits that Altace was approved by the FDA and manufactured under the ‘258 patent, which included the compound Ramipril not substantially free of other isomers. The Court, as it has said several times, is not convinced one way or the other that “substantially free of other isomers” accomplishes anything. It certainly has no evidence that Altace’s isomeric purity – a unique characteristic of Ramipril, according to Aventis/King – is connected in any way to Altace’s commercial success. In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996) (stating that commercial success is “relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention”).

There is substantial evidence that Altace became commercially successful as a result of an intensive marketing campaign based on the HOPE Study. This is not to say that the HOPE Study is invalid. Indeed, it appears to be a very good study with a good outcome for Altace. What is apparent, however, is that the HOPE Study was heavily marketed to the medical community by means of a mighty sales force and sales consequently rose as a result of an expensive outlay.<sup>23</sup> See supra II.F. (findings related to Aventis/King’s marketing efforts). Moreover, given that, from 1998 to 2005, Altace was protected by the ‘258 patent as well as the ‘722 patent and market entry by others was therefore precluded, the inference of non-obviousness because of commercial success is weak and the Court finds it non-existent. Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005) (finding weak commercial success when patents kept other competitors from the market). “Commercial success is relevant because the law presumes an idea would

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<sup>23</sup>The world is replete with examples of advertising and the effects of it, and the situation before the Court here is no different. Mr. Hill, the famous CEO advertiser, increased Lucky Strikes’ sales by 38% in six weeks with his phrase “Lucky Strike Green has Gone to War.” In Freakonomics, the authors similarly describe how Listerine dramatically increased its sales by essentially inventing halitosis. STEVEN D. LEVITT & STEPHEN J. DUBNER, FREAKONOMICS (HarperCollins 2005).

successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art.” Id. at 1376. When an idea cannot be brought to market sooner because a patent stands in the way, the rationale for finding commercial success becomes much less. Id.

Second, with respect to the secondary consideration of “long-felt need,” there is little question that there were several effective ACE-inhibitors on the market before Altace entered the market. See Monarch Knitting Mach. Corp. v. Fukuhara Indus. & Trading Co., Ltd., 139 F.3d 877, 884 (Fed. Cir. 1998) (explaining that whether an invention fulfilled a long-felt need is evidence of nonobviousness). There was simply no “long-felt need” for another ACE-inhibitor. As the cross-examination of Dr. Scholkens pointed out, Enalapril and Ramipril are equipotent when administered intraduodenally. See supra II.D.3. As for the HOPE Study indication, the Court is not convinced that Altace performs better than other ACE-inhibitors in preventing heart attacks in high-risk patients because the HOPE Study tested Altace against a placebo. See supra II.E. Enalapril, for example, whose potency was equal to Ramipril’s when administered intraduodenally, apparently has not yet been tested for this result. The other drugs studied and cited by Aventis/King were tested on different populations. Moreover, there is nothing in the ‘722 patent related to preventing heart attacks in high-risk patients. Ortho-McNeil, 348 F. Supp.2d 713, 758 (N.D. W.Va. 2004) (“Evidence of the existence of a long-felt need may be found, among other places, in the prior art, . . . or in the patent itself.”). Consequently, the Court is simply not persuaded that Altace is meeting a “long-felt” need.

As for copying, there is no question that Lupin attempted to copy Altace. That is what generic drug companies do. That is why their products are cheaper. As MOY’S WALKER ON PATENTS observes, however, “[the copying] rationale is considerably weakened . . . by the fact that

there are various other reasons why an invention may have been copied.” § 9:60 (4th ed. 2005). In this case, the reason why Lupin attempted to copy Altace is because the ANDA process allows a generic drug company to challenge a drug patent by alleging the patent is invalid. Aventis Pharma Deutschland GMBH v. Lupin Ltd., 403 F. Supp.2d 484, 486 (E.D. Va. 2005) (explaining the “paragraph IV” provision and the ANDA process). Accordingly, given that there is a statute in place that encourages generic drug companies to challenge patents, Aventis/King’s copying argument is weak.

Finally, the Court is not persuaded that the evidence shows that Altace indicates “unexpected results.” For example, Dr. Scholken’s indication that Ramipril substantially free of other isomers had an ACE-inhibiting activity of about three times greater than Enalapril resulted from the drugs being given to dogs after intravenous injection. See II.D.13. Although not included in his Declaration before the PTO, however, Dr. Scholkens testified in this case that Ramipril and Enalapril were “approximately equipotent” after intraduodenal administration. Id. When asked why he did not include this information in his Declaration before the PTO, Dr. Scholkens stated “the declaration is not a scientific paper.” The Court thus has some doubt that Ramipril substantially free of other isomers was as “far superior” to Enalapril as Dr. Scholkens suggested, as he withheld certain information because his declaration was not a “scientific paper.”<sup>24</sup> Thus, what he maintains is a “scientific conclusion” is not a “scientific paper.” In addition, although there is no question that the 5(S) isomer of Ramipril is preferred, there is some question as to whether it is preferred in isolation as opposed to a mixture. The Court has said many times it has found no evidence to support a conclusion one way or the other. This open question as to the value of Ramipril being “substantially free of other isomers” causes the Court to question Aventis/King’s claims of “unexpected results.”

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<sup>24</sup>This merely emphasizes the need for cross-examination of paid advocates.

Finally, the HOPE Study indicated, unquestionably, that Altace was found to prevent heart attacks, strokes, and diabetes. As the Court has noted, however, the drug was not tested against other drugs – it was tested against a placebo. Nor did the tests include Enalapril, which was equipotent in the high-blood pressure context. This is perhaps why the American College of Cardiology does not single out Altace in its guidelines regarding the treatment of chronic stable coronary disease. Wharton at 723: 12-16; Def.’s Ex. 610. If there is no clinical indication designating Altace over any other ACE-inhibitor for this purpose, the Court has a difficult time concluding that the HOPE Study indicated unexpected results by being substantially free of other isomers.

### **C. Enablement/Lack of Written Description**

“[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Under 35 U.S.C. § 112, ¶1,

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

When determining enablement, “[t]he specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without ‘undue experimentation.’” Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1334 (Fed. Cir. 2003).

Lupin’s first argument with respect to enablement essentially rests upon asking this Court to apply the same standards of enablement to the Schering References as it would to the ‘722 patent.

See Def.'s Trial Br. at 33. In other words, if the Court had found that the '944 and '258 patents were not enabled for the reasons Aventis/King urged, then the same reasons should be applied to the '722 patent. Given that the Court has found that Schering References and the '258 patent were enabled, Lupin's concerns in this regard have been addressed.

Lupin goes on to maintain that the specification of the '722 patent provides no guidance as to when a compound qualifies as being "substantially free of other isomers." Def.'s Opening Tr. Br. at 7. The problem with Lupin's argument is that it has urged, throughout this case, that it would have been obvious to one of ordinary skill in the art to separate Ramipril isomers until the 5(S) configuration was accomplished. Thus the Court has a difficult time accepting the argument that a person of ordinary skill in the art would not be enabled, without undue experimentation, to make Ramipril in the 5(S) configuration substantially free of other isomers.

Lupin makes a good point that "substantially free of other isomers" is easily defined legally, as the Court did in its Claim Construction Order, but much harder to define scientifically. In other words, the Court has indeed wondered, throughout this case, what "substantially free of other isomers" actually accomplishes for Ramipril. The problem is that this question of whether a portion of the invention matters has nothing to do with whether a patent is enabled – it is a question of indefiniteness. While Aventis/King has not convinced this Court that "substantially free of other isomers" makes a bit of difference, Lupin did not convince this Court that the phrase is fatally indefinite either, as the Court found that "'substantially free of other isomers' is not indefinite given its plain-meaning and the fact that it would indicate to a person of ordinary skill in the art that the compound was largely free of other isomers but not 100% pure." See Claim Construction Order at 24-26.

Finally, the fact that the Court found that Lupin's Ramipril capsules with up to 0.50% of

Isomer-1 infringed the '722 patent under the doctrine of equivalents does not change this Court's view in regards to any of its rulings. When it found infringement based on the doctrine of equivalents, the Court, indeed, concluded that it is Ramipril – the active ingredient – that mattered under that analysis. The problem for Lupin now is that Aventis/King has effectively raised enough questions in this Court's mind about whether the purity of Ramipril in the 5(S) configuration also matters. This is a different question from whether Lupin's version of Ramipril was essentially the same as Aventis' Altace. If the preponderance of the evidence standard was the standard to judge this case, the Court might agree with Lupin, but, as the Court has said many times, that is not the standard to be applied here since the '722 patent was granted. A patent is presumed valid and invalidity must be shown by clear and convincing evidence.

#### **IV. Conclusion**

Obviously, although the Court is finding for Aventis/King, it has reservations in doing so. Using common sense, and not the intricacies of patent law, the bottom line is that Altace is going to be on the market for approximately two years longer than it probably should be because it was first approved under the '258 patent, which has expired.<sup>25</sup> But the Court applies the law – not necessarily

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<sup>25</sup>Indeed, Aventis/King does not dispute that Altace – the Altace they have been selling all along – was first approved under the '258 patent.

The Court:                    You know, Mr. Katcoff, [attorney for Aventis], something worries me about this entire matter. And what really gave me some concern is you were manufacturing Altace. Under the '258 patent. . . Isn't that correct?

Mr. Katcoff:                We were manufacturing --

The Court:                    Is that correct?

Mr. Katcoff:                Under the '258 patent, absolutely correct. But the '258 patent is a

common sense.

In the Court's view, this case involves a circumstance that is not adequately addressed by the ordinary validity tests of anticipation, obviousness, and enablement. No factor under any of these tests allows the Court to consider the fact that the very same product appears to have been approved and made first under one patent and then later under another patent. But evaluating the patents outside of the products approved by the FDA and the products manufactured under them results in an outcome that effectively allows one product – Altace – to have approximately two more years of patent protection than it probably should have.

In addition, although inequitable conduct might have occurred, the Court is very much aware that Aventis/King may simply be taking advantage of happenstance. Clearly, Aventis fought hard to make and produce Altace and, to cover its bases, both licensed the '258 patent from Schering and simultaneously pursued its own patent. There is nothing inequitable or wrong about doing that. As soon as it received a license from Schering, it went to the FDA for the approval of Altace. If it had received the '722 patent first, it undoubtedly would have gone to the FDA for approval using that patent. The fact, however, that the '722 patent was approved subsequently to the '258 patent has allowed Aventis to maintain, at this point in time, that Altace falls under the '722 patent and not the '258 patent. When Aventis was pursuing the '722 patent in the 1980s and early 90s, there is no evidence that it intended this result. Rather, the timeline that resulted from Aventis' efforts now works in its favor. Considering the high standard of clear and convincing evidence required to set aside the '722 patent, Lupin's effort fails and the '722 patent remains in effect and is therefore valid in so far as this case is concerned.

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different story. It is not prior art. Not prior art.

See Closing Arguments Trans. at 33-34.

With that said, the Court must observe that Aventis' arguments with respect to the '258 patent in this matter are plainly inconsistent with its representations to the PTO and FDA. There is no question that Aventis, after licensing the '258 patent from Schering, obtained FDA approval to market Ramipril using the trade name Altace and that it also obtained an extension of the '258 patent from the PTO representing that the '258 patent covered "the sole active ingredient" in Altace. This is what gives the Court concern. The problem for the Court is that it has been persuaded that there is no proof of clear and convincing evidence that the '722 patent is invalid. The other problem is that inconsistency and clever lawyering do not necessarily constitute misrepresentation on the part of the inventors.

In addition, while Aventis points out that there are several drugs where both the species and genus are listed in the FDA's Orange Book, the Court wonders whether these species and genres were listed simultaneously or, as is the case here, at different times.<sup>26</sup> More importantly, this seems to be an FDA problem rather than a PTO problem. Or, more specifically, it seems to be a problem with the Hatch-Waxman ANDA process, as the simple filing of a patent in the Orange Book puts an entire patent litigation process in motion. In other words, if it is common for species and genera to be listed at different times yet cover the same drug, then drug manufacturers may indeed use the Orange Book to protect that drug from competition – they are essentially extending patent protection by means of the FDA and not the PTO. Solving these policy problems, however, is not the Court's role but the role of Congress.

Indeed, the anomaly presented by this case is that Lupin may not manufacture the Ramipril

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<sup>26</sup>Plaintiff King pointed out in closing arguments that, in Pfizer Inc. v. Ranbaxy Labs Ltd., 405 F. Supp.2d 495 (D. Del. 2005), the district court concluded that the species was patentable over the genus and noted that both the species and genus have different expiration dates. It is unclear to this Court, however, if both the genus and species were listed in the Orange Book and when.

that Aventis licensed with the FDA under the ‘258 patent, even though that patent has expired, because of the doctrine of equivalents as applied with respect to the ‘722 patent. Aventis candidly indicates that they applied for FDA approval under the ‘258 patent to manufacture and market Ramipril substantially free of other isomers as the ‘722 patent had not yet been granted. Thus from technical and clever maneuvering Aventis has lengthened its monopoly to the detriment of the public. In reality, the ‘722 patent should not under these circumstances be any longer than the ‘258 patent – in other words, both patents should have expired at the same time. Clearly, the pharmaceutical lobbyists have won this round.

Finally, even though no one appears to know (or be able to admit) whether Ramipril “substantially free of other isomers” makes any therapeutic difference, the fact is that open question raises enough doubt in the Court’s mind for it to be unable to find for Lupin under the clear and convincing evidence standard. The ‘722 patent unquestionably patents Ramipril as a compound in an essentially pure molecular form, namely in the 5(S) configuration “substantially free of other isomers.” The ‘258 patent unquestionably does not, and Lupin has not shown, by clear and convincing evidence, that the purity of Ramipril – the essential isolation of Ramipril in the 5(S) configuration – was anticipated or obvious. It is quite possible that the ‘722 patent should have never been granted, but once it was granted, attacking its validity is a very difficult task indeed. Unfortunately, the law is the law.

The Court **FINDS** for the Plaintiffs. Accordingly,

- The Court **FINDS** that Lupin has failed to prove, by clear and convincing evidence, that the ‘722 patent is invalid;
- The Court **DECLARES** that making, using, selling, offering to sell, and/or importing the Ramipril capsules described in Lupin’s ANDA application constitutes infringement of the ‘722 patent;
- The Court **ENJOINS** Lupin, its officers, agents, servants and employees

from making, using, offering to sell, selling, or importing the Ramipril capsules described in its ANDA application until the expiration of the '722 patent; and

- The Court **ORDERS** that the effective date of the products described in Lupin's ANDA application shall not precede the expiration of the '722 patent.<sup>27</sup>

The Clerk is **DIRECTED** to send by facsimile and United States mail a copy of this Order to all counsel of record.

**IT IS SO ORDERED.**

\_\_\_\_\_/s/\_\_\_\_\_  
Robert G. Doumar  
UNITED STATES DISTRICT JUDGE

Norfolk, Virginia  
July 17, 2006

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<sup>27</sup>Under 35 U.S.C. § 271(e)(4), the remedies available to a plaintiff that successfully protects its patent in ANDA cases are:

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product, and

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product.